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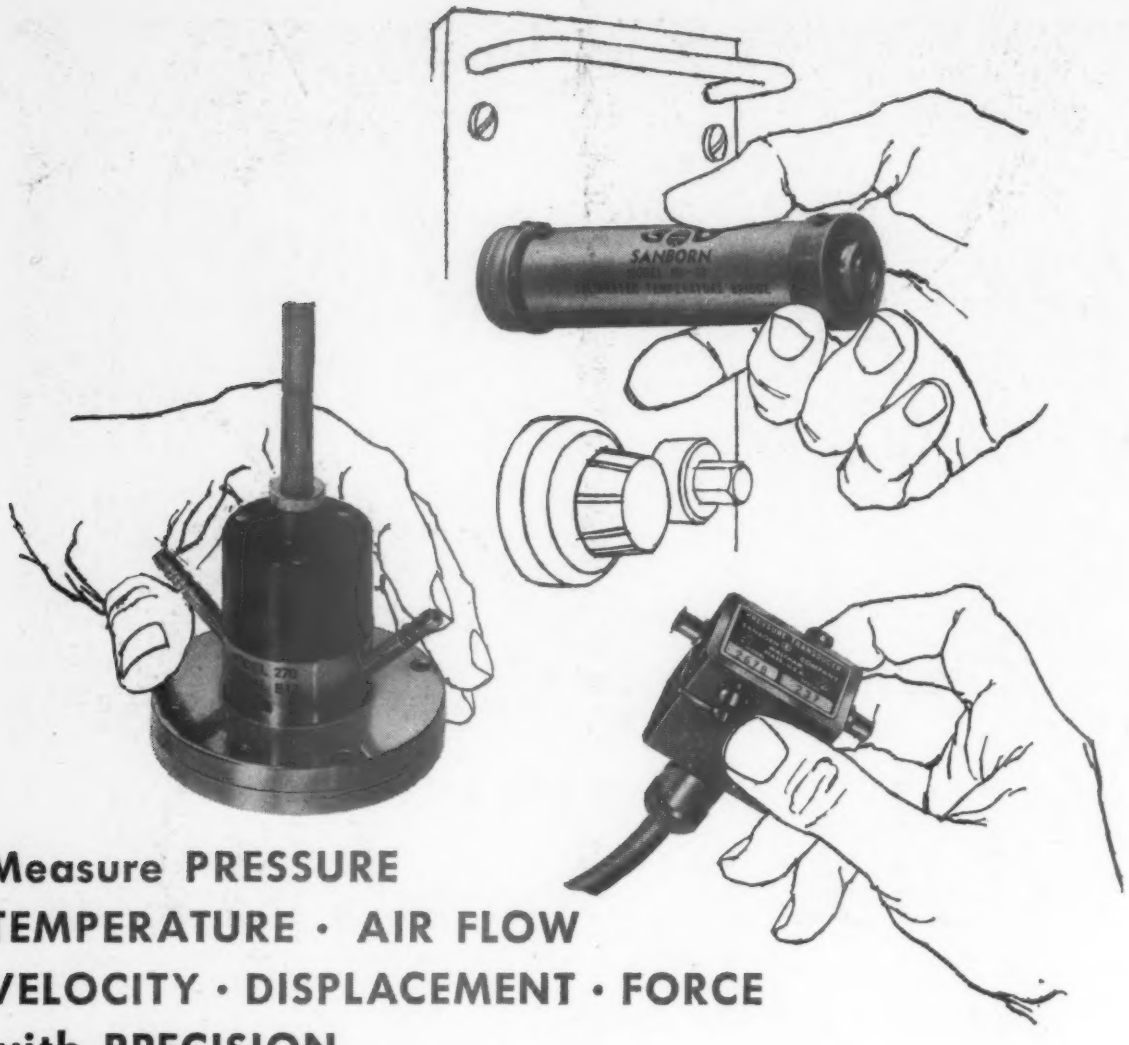

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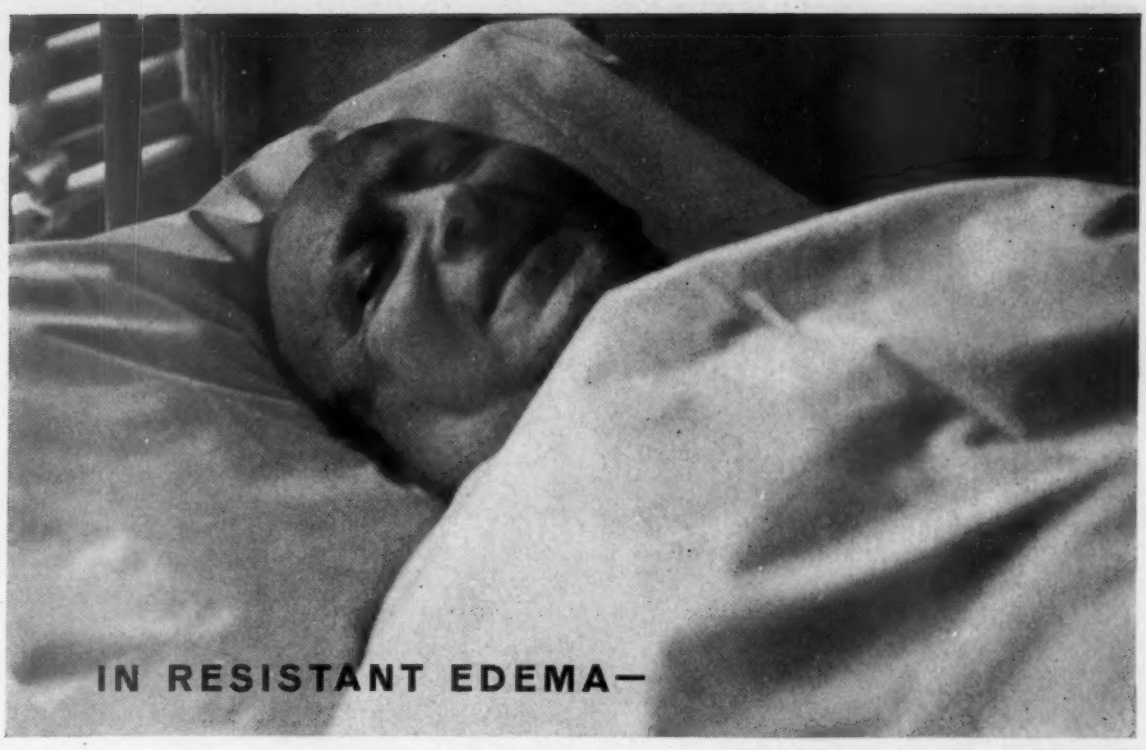

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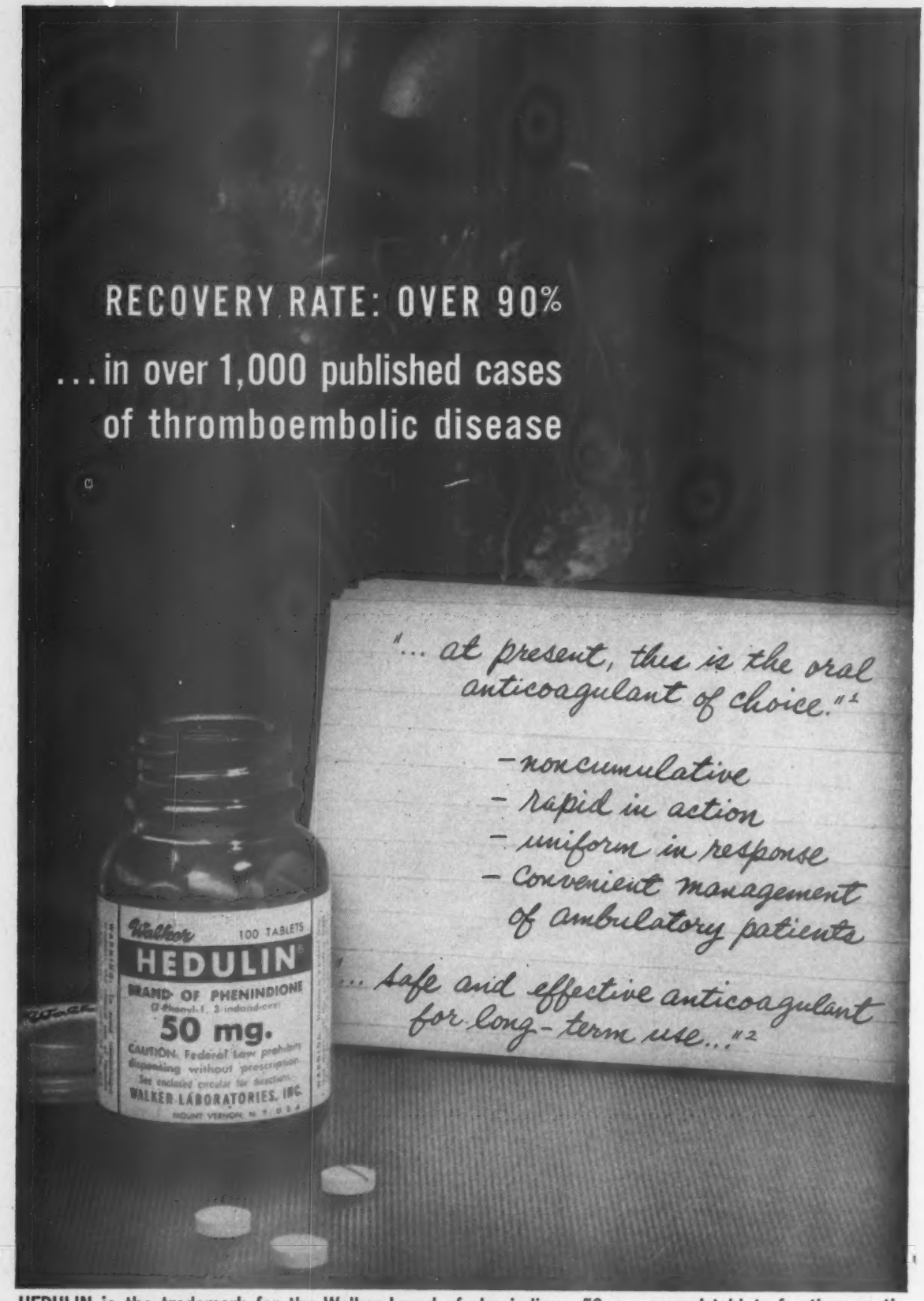
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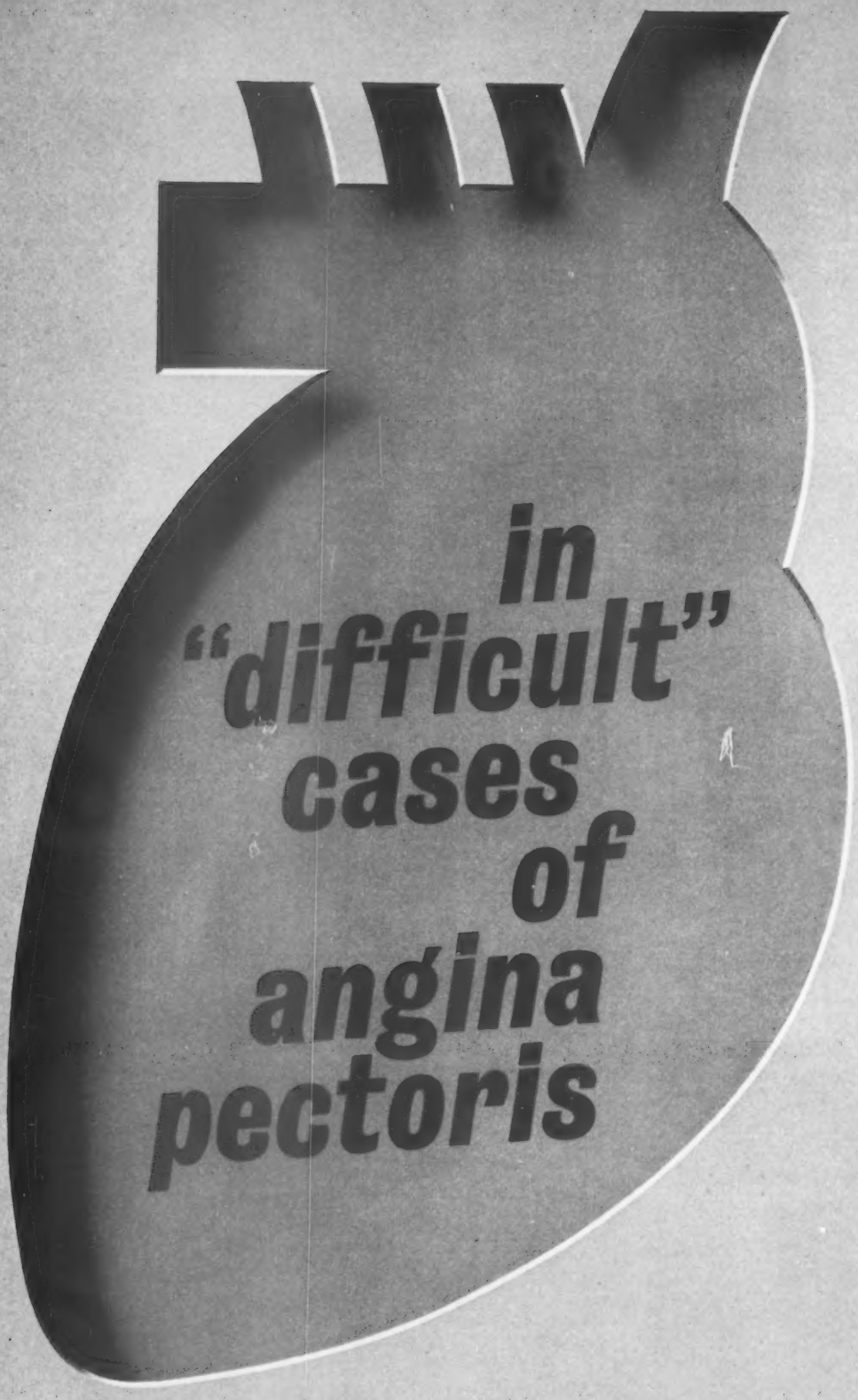

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LEONARD J. FEINBERG, HERSCHEL SANDBERG, EDWARD R. DICKSTEIN AND SAMUEL BELLET

Intravenously administered I^{131}-triolein disappeared from whole blood and circulating lipoproteins equally fast in the control group and in patients with myocardial infarction, but more slowly in patients with hypothyroidism and primary amyloidosis. These studies suggest that the primary defect in myocardial infarction may be intimately linked up with absorption of neutral fat.

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By recording the arterial sounds, quantitative data were obtained and the duration of these vibrations with relation to variations in blood pressure, exercise and following tourniquet application were recorded. Reactive vasodilation results in marked increase in duration, whereas obstruction of blood flow shortens duration of arterial sounds.

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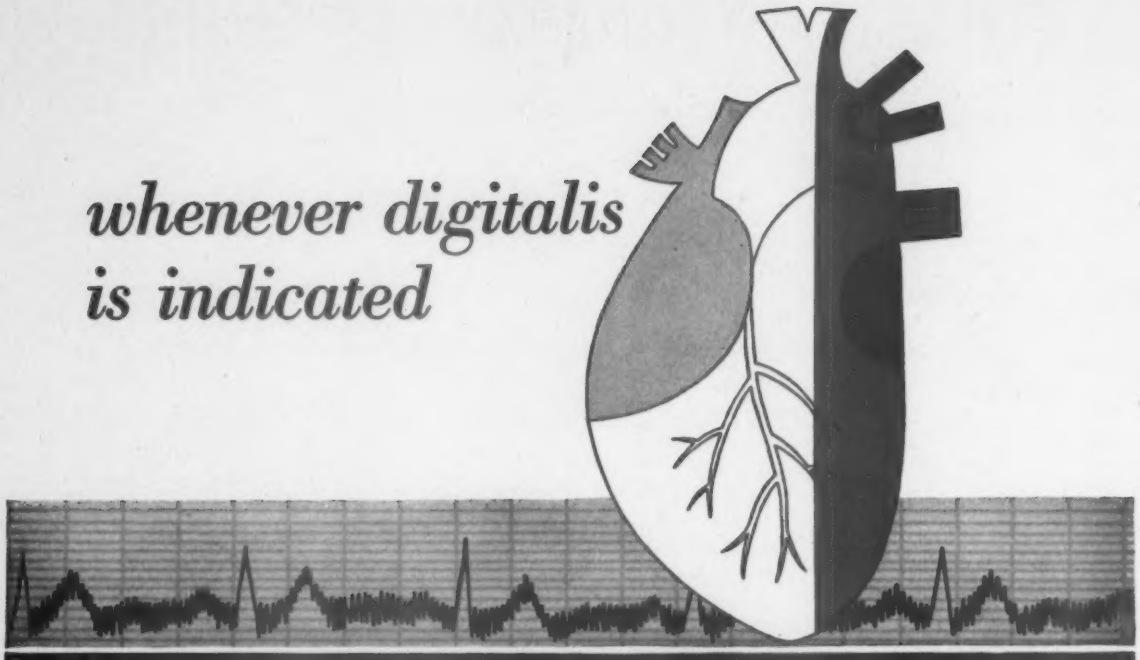

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in coronary artery disease

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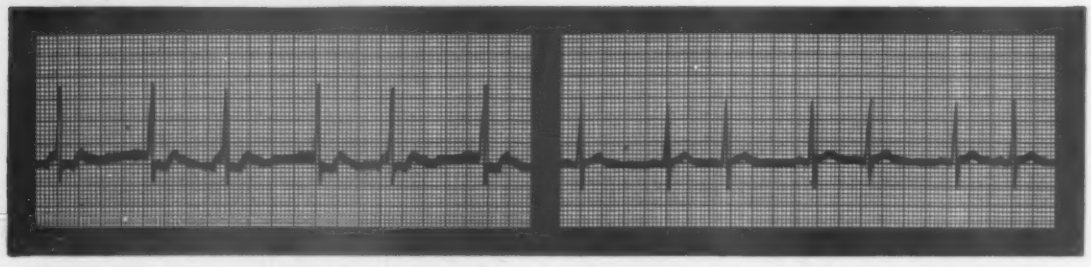
the patient with angina*



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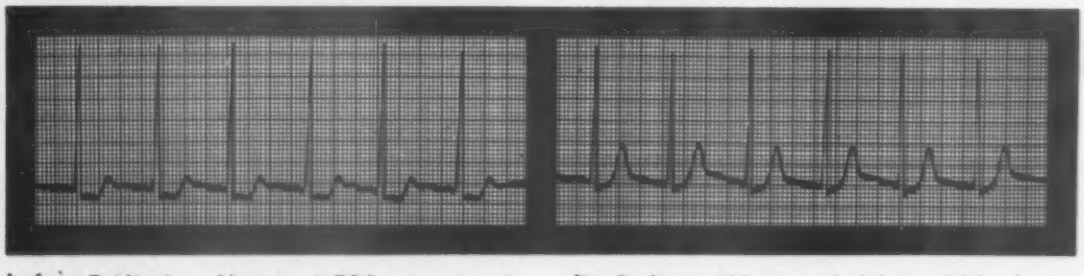
the postcoronary patient without angina*



before **Peritrate**—Abnormal ECG response to standard exercise in postinfarction patient without angina.

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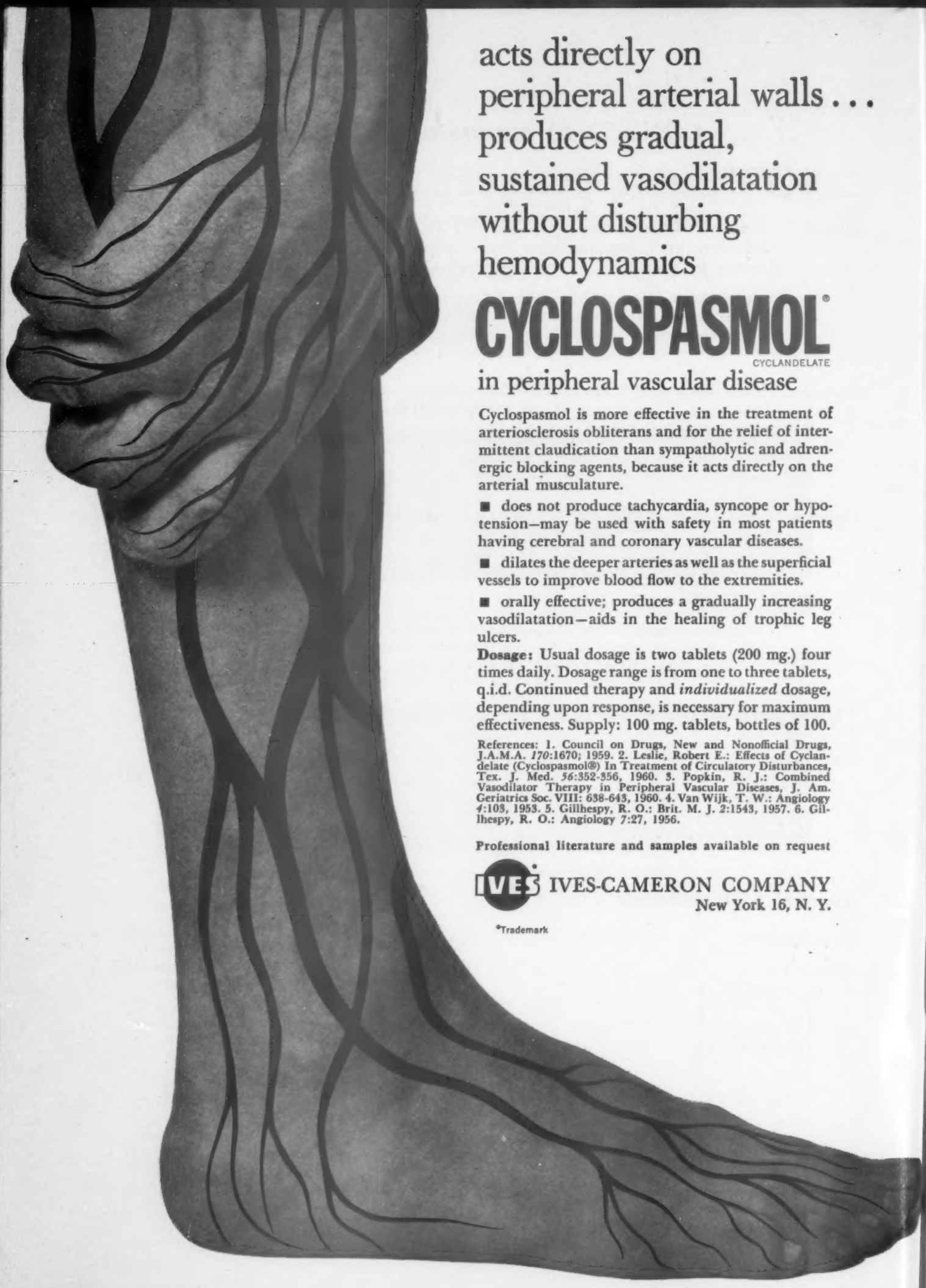

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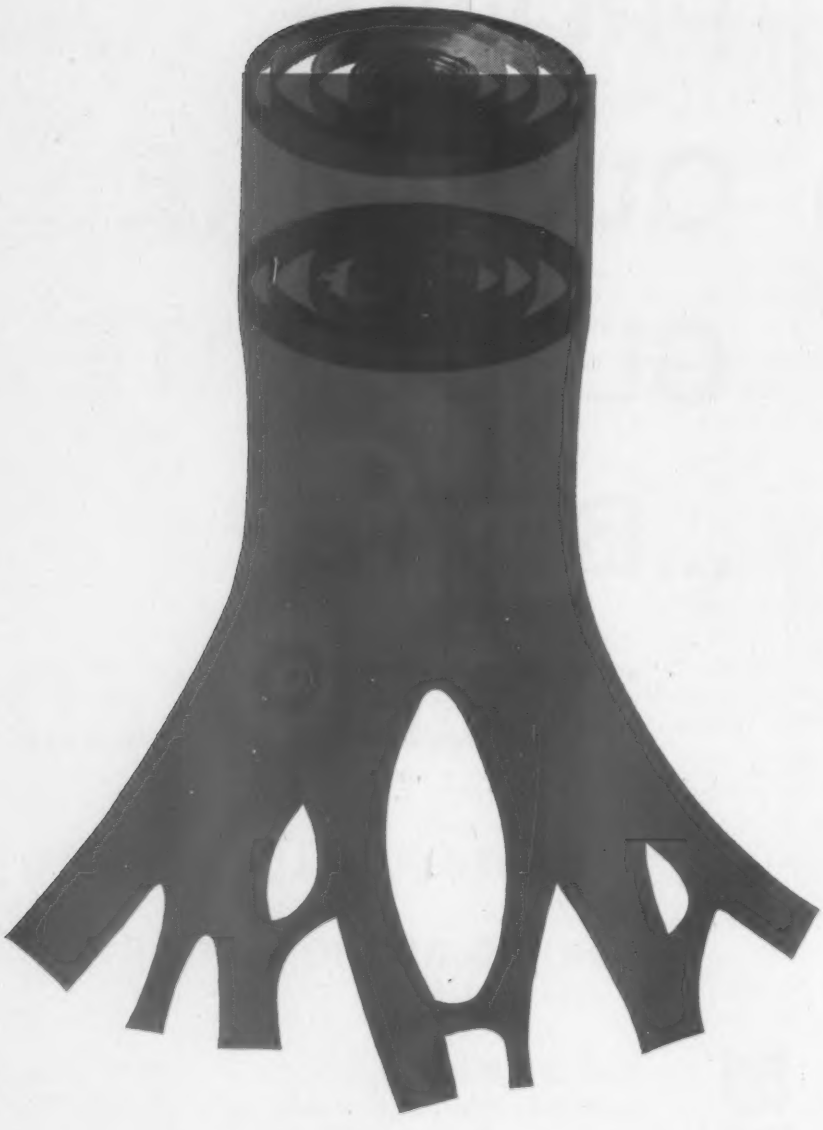

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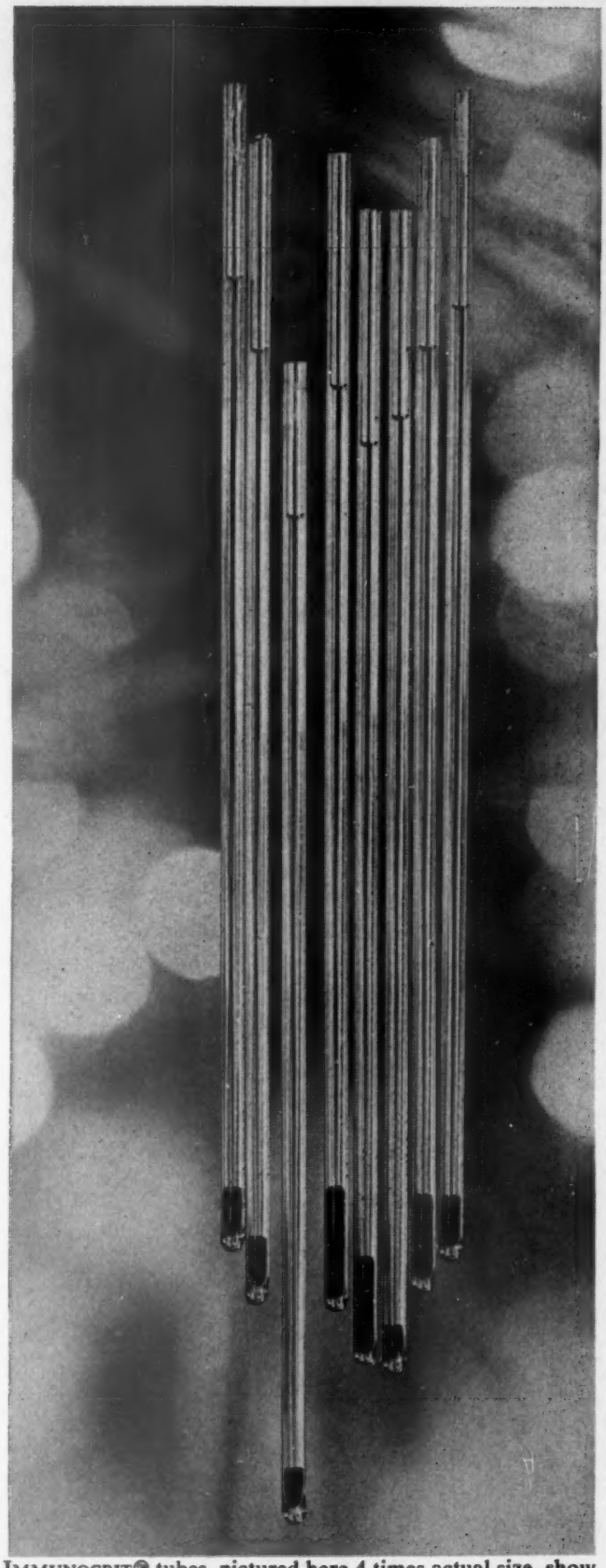

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2. Heiskell, C. L., Fisk, R. T., Florsheim, W. H., Yachi, A., Goodman, J. R., and Carpenter, C. M.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222 (March) 1961.

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references: (1) Hirshleifer, I.: Adjunctive Therapy in Cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961.
(2) Frohman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, **ibid.**
(3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, **ibid.**

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1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:118, Sept. 10, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

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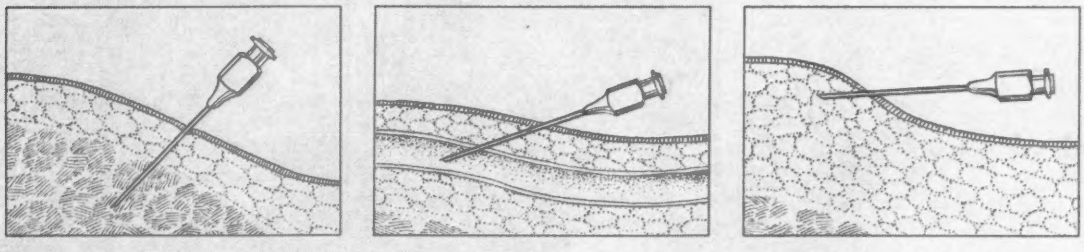

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References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: in Drugs of Choice, C. V. Mosby Co., St. Louis, 1960, p. 419. 3. Kayden, H. J., et al.: Med. Concepts Cardiovasc. Dis. 20:100, 1951. 4. Miller, H., et al.: J.A.M.A. 145:1004, 1951.

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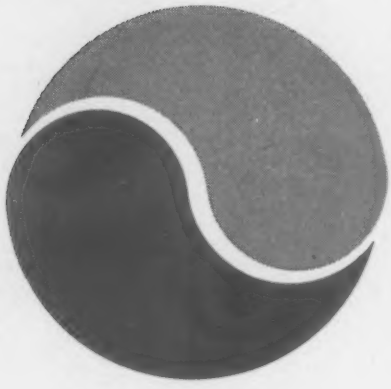

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REFERENCES: 1. Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Peiner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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The American Journal of Cardiology

VOLUME VIII JULY 1961 NUMBER 1

Clinical Studies

Disappearance Curves of Intravenously Administered I^{131}-Triolein in the Human Subject*

LEONARD J. FEINBERG, PH.D., HERSCHEL SANDBERG, M.D., EDWARD R. DICKSTEIN, M.D. *and* SAMUEL BELLET, M.D., F.A.C.C.

Philadelphia, Pennsylvania

I^{131}-LABELED triglycerides have been extensively used to investigate neutral fat metabolism in pathologic states since 1949 when Thannhauser and Stanley[1,2] fed I^{131}-labeled olive oil to patients and measured the appearance and disappearance of the radioactivity in the blood. During the past decade this method has been utilized to demonstrate malabsorptive states secondary to chronic pancreatitis, sprue, carcinoma of the pancreas and extensive bowel surgery. These states are characterized by low levels of radioactivity in the whole blood and its circulating lipoprotein fraction, after ingestion of a test meal.[3–6] Hyperlipemic states have also been investigated by this technic.[4,7] Recent studies[7–9] from this and other laboratories have shown that patients with coronary artery disease have abnormal oral triolein tolerance curves. Following the ingestion of a test meal containing I^{131}-triolein, the radioactivity of the whole blood, the circulating lipoprotein fraction and the percentage of the whole blood radioactivity present as lipoprotein have been found to be considerably higher than those of normal controls. This elevation persists for at least twenty-four hours.[7] In a more recent study of another population prone to the early development of atherosclerotic complications, patients with diabetes mellitus, similar abnormal I^{131}-triolein tolerance curves were obtained, even in subjects who showed no clinically demonstrable signs of atherosclerotic complications.[10] Since these curves are the resultant of "possible pathologic variations of a poorly understood physiologic process" in which absorption as well as metabolic transport and oxidation play important roles,[11] it was decided to attempt to localize further this abnormality in lipid metabolism, bypassing the absorptive phase entirely by means of intravenous administration of I^{131}-triolein. The curves resulting from such a procedure are the subject of this report.

MATERIAL AND METHODS

Patient Population: The patient population consisted of eighteen subjects from the medical wards of the Philadelphia General Hospital. Nine of these had no known lipid abnormality. Five had proven myocardial infarction by both clinical history and electrocardiogram. Three patients had signs of advanced hypothyroidism and one was found at autospy to have primary amyloidosis of the heart. A detailed

* From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Robinette Foundation of the University of Pennsylvania. This work was supported by the United States Public Health Service, Grant H4153 (National Heart Institute).

TABLE I

Intravenous I^{131}-Triolein Whole Blood and TCA* Disappearance Curves

Case No.	Age (yr.) and Sex	Weight (lb.)	Diagnosis	Whole Blood Activity (min.)			TCA Activity (min.)		
				Time of First Minimum Activity	Duration of Rise	Duration of Elevation Above First Minimum	Time of First Minimum Activity	Duration of Rise	Duration of Elevation Above First Minimum
			A. Control Group						
1	24, F	105	Chronic pancreatitis	15	20–60	20–180	20	30–40	30–80
2	23, F	98	Hepatitis	15	20–60	20–180	20	30–40	30–60
3	39, M	141	Peptic ulcer	60	80† 120‡	80† 120‡	100	120	120–180
4	40, M	120	Pulmonary tuberculosis	12.5	15–80	15–120	12.5	15	15
5	38, M	115	Pulmonary tuberculosis	15	20–40† 100‡	20–180	120	137	137
6	35, F	130	Pulmonary tuberculosis	20	30† 140‡	30–60	120	140	140
7	31, M	174	Pulmonary tuberculosis	20	30	30–40	None	None	None
8	36, F	139	Mitral stenosis cerebral embolus	17	30–60	30–150	30	60	60
9	78, F	...	...	21	15–60	15–180	120	150	150
			B. Myocardial Infarction Group						
10	61, F	145	Myocardial infarction	15	24–60	24–180	24	30	30–40
11	55, M	192	Myocardial infarction	15	20–32	20–180	20	32	32–40
12	75, M	122	Myocardial infarction	15	20–60	20–180	20	30–40	30–60
13	67, M	200	Myocardial infarction	20	30–40	30–180	30	30	30
14	40, M	182	Myocardial infarction	15	20–60	20–90	None	None	None
			C. Myxedema Group						
15	67, M	194	Myxedema	30	60† 120‡	60† 120‡	10	12	12
16	75, F	120	Myxedema	30	40–80	0–160	30	40	40
17	48, M	147	Myxedema	20	30	30	80	100	100
			D. Primary Amyloidosis						
18	64, M	140	Primary amyloidosis of heart	None	None	None	180	240	240

* Lipoprotein fraction precipitated by 20 per cent trichloroacetic acid. † Period of rise following first minimum. ‡ Period of rise following second minimum.

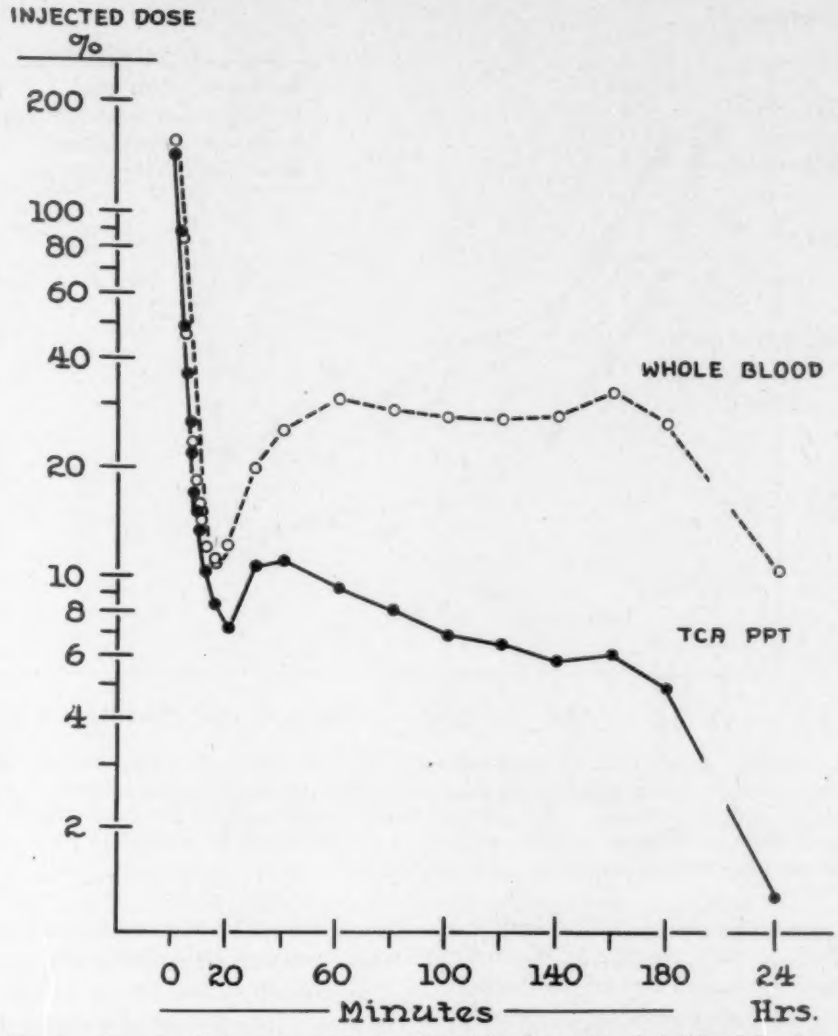

FIG. 1. Case 1. Disappearance of radioactivity from the whole blood (broken line) and its circulating lipoprotein fraction (solid line) in a normal control subject who had received 75 μc. of I^{131}-triolein intravenously. The ordinate expresses the radioactivity as per cent of injected dose (estimating the blood volume as 7.7 per cent of body weight). The abscissa shows the time in minutes after injection of the radioactive material.

description of age and weight distribution is presented in Table I.

Preparation of Emulsion for Intravenous Administration: I^{131}-triolein was prepared for intravenous administration in the following manner: 50 to 100 μc. of I^{131}-triolein were added to one volume of an anhydrous lipid emulsion "pre-mix" as described by McCandless and Zilversmit,[12] and mixed in a Vertis homogenizer for four minutes at 23,000 r.p.m. The mixture obtained was diluted with 9 volumes of a 5 per cent dextrose solution and re-emulsified. The preparation was sterilized by pressure filtration through a Millipore* filter and re-emulsified under aseptic conditions just prior to injection. Emulsions prepared in this manner were tested for sterility. No bacterial growth occurred in ten days. Samples were also examined microscopically for particle size. The average particle size was below the limit of the light microscope and all particles were less than 4 μ. As a further precaution, the first studies with this emulsion were made on patients in the terminal stages of their disease, with a life expectancy of a few weeks. No adverse reactions were noted.

Test Procedure: A Cournand needle was inserted into the anticubital vein of the patient. Into the anticubital vein of the contralateral arm, approximately 5 gm. of the prepared mixture containing about 75 μc. of I^{131}-triolein were rapidly injected. Timing was started at the midpoint of the injection and samples were drawn into heparinized tubes at the following intervals: Every minute for the first ten minutes, then at twelve, fifteen, twenty, thirty and forty minutes. Thereafter, samples were drawn at twenty minute intervals until 180 minutes after injection. A twenty-

* Millipore Filter Corp., Bedford, Massachusetts.

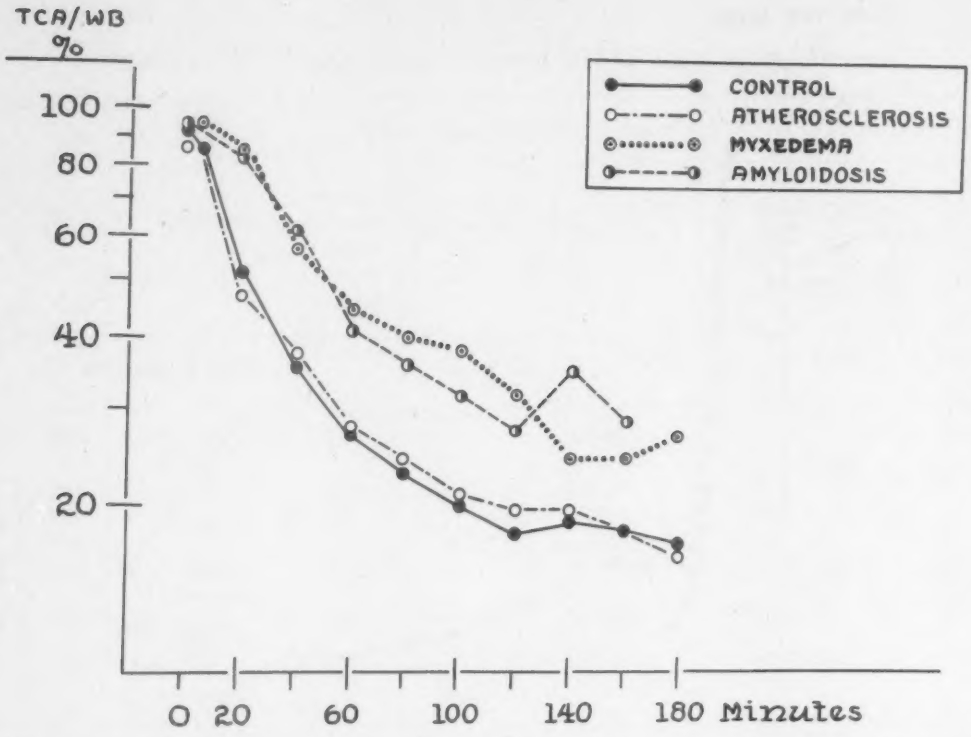

FIG. 2. Change in the ratio of lipoprotein I^{131} to whole blood I^{131} (TCA/WB) with time following the intravenous administration of I^{131}-triolein to the following subjects: (A) normal control subjects (mean); (B) patients with recent myocardial infarction (mean); (C) myxedematous subjects (mean); and (D) a patient found at autopsy to have primary amyloidosis of the heart (Case 18).

four hour sample was also drawn. Two milliliter aliquots of these samples were pipetted in duplicate. One of these (WB) was counted directly for radioactivity in a well-type scintillation counter; the other aliquot was precipitated with 20 per cent trichloroacetic acid (TCA) after addition of carrier iodide. The precipitate was washed twice with 5 per cent TCA and analyzed for radioactivity in a manner previously described.[7] The radioactivity of the samples is expressed as per cent of administered dose based on an estimated blood volume, in the whole blood and circulating lipoprotein (TCA precipitable) fraction. The patients were observed clinically during the next few days for evidence of fever, pain in the back, or other evidence of "colloid reactions" to the intravenous fat injection.

Curves of the log of the whole blood activity (WB), circulating lipoprotein activity (TCA), and the fraction of whole blood activity present as circulating lipoprotein (TCA/WB) were plotted against time. From these the time for a given amount of radioactivity to fall to half its original level ($T^1/_2$) was estimated.

RESULTS

CONTROL GROUP

Disappearance of Radioactivity from the Whole Blood: The disappearance of the radioactivity from the whole blood and its circulating lipoprotein fraction is shown in Figure 1 and Table 1. The whole blood (WB) radioactivity curve is complex, consisting of a rapid initial disappearance phase during the first five minutes with a $T^1/_2$ of two to four and a half minutes, a slower rate of fall during the next five to seven minutes, reaching a minimum at about fifteen minutes. It then rises again for a variable interval until sixty minutes after injection of the isotope and then slowly falls again. Usually the activity remains higher than the first minimum for two to three hours.

Disappearance of Circulating Lipoprotein Radioactivity from the Blood: The circulating lipoprotein curve (Fig. 1) parallels the whole blood activity curve for the first five to seven minutes, but then falls at a more rapid rate than the whole blood radioactivity. It usually does not start to rise until thirty minutes or later and the rise lasts for a shorter interval than the whole blood radioactivity. It rarely remains higher than the first minimum for more than twenty minutes.

Curve of TCA/WB: Curves of the fraction of the whole blood present as circulating lipoprotein are shown in Figure 2. It can be seen that

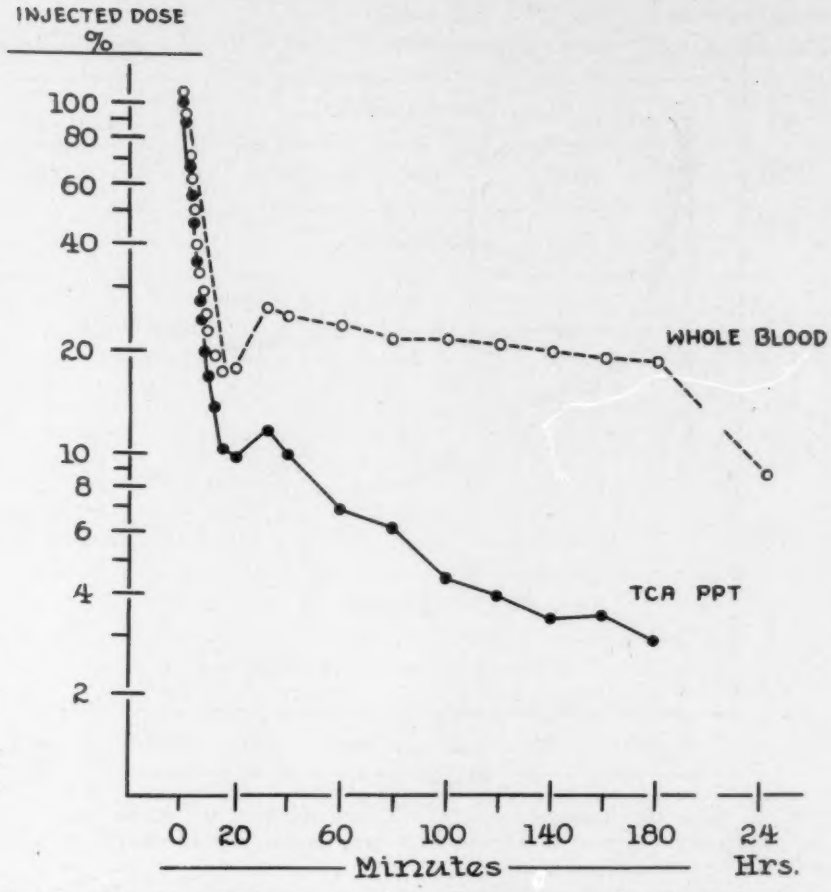

FIG. 3. Case 11. Typical curve of the disappearance of radioactivity from the whole blood (broken line) and its circulating lipoprotein fraction (solid line) in a patient with acute myocardial infarction.

this ratio drops very slowly during the first five to six minutes. During the next fifteen minutes it falls very rapidly until twenty minutes after injection of the isotope when the ratio steadily diminishes, but at a slower rate, until the first hour and begins to level off about two hours after injection of the isotope (Table II).

MYOCARDIAL INFARCTION

The disappearance curves obtained in the patients with myocardial infarction (Fig. 3 and Table I) did not differ significantly from those of the control group.

MYXEDEMA

In the patients with myxedema the curves differ from those just described. In the whole blood and TCA fractions the peak levels are not reached until two to three minutes after injection of the isotope and they disappear from the blood stream at a much slower rate (Fig. 4). In the curve TCA/WB (Fig. 2) the fraction of whole blood radioactivity bound to protein disappears much more slowly during the sixth to twentieth minute interval, remaining well over 60 per cent of the total radioactivity during this period (Table II).

AMYLOIDOSIS

In one patient, found to have primary amyloidosis of the heart at autopsy, a delay in clearance of the radioactivity similar to that seen in myxedema, particularly the fraction bound to protein, was noted (Table II).

COMMENTS

Difficulties Attending the Intravenous Use of Radioactively Labeled Fat Emulsions: At the present time there is no commercially available radioactively labeled triglyceride emulsion suitable for intravenous use in human beings.* The nonradioactive preparations commercially available

* Since this work was completed, Abbott Laboratories has recently made available (for investigative use) a preparation of I^{131}-labeled triolein suitable for intravenous administration. Studies are now in progress to determine its efficacy.

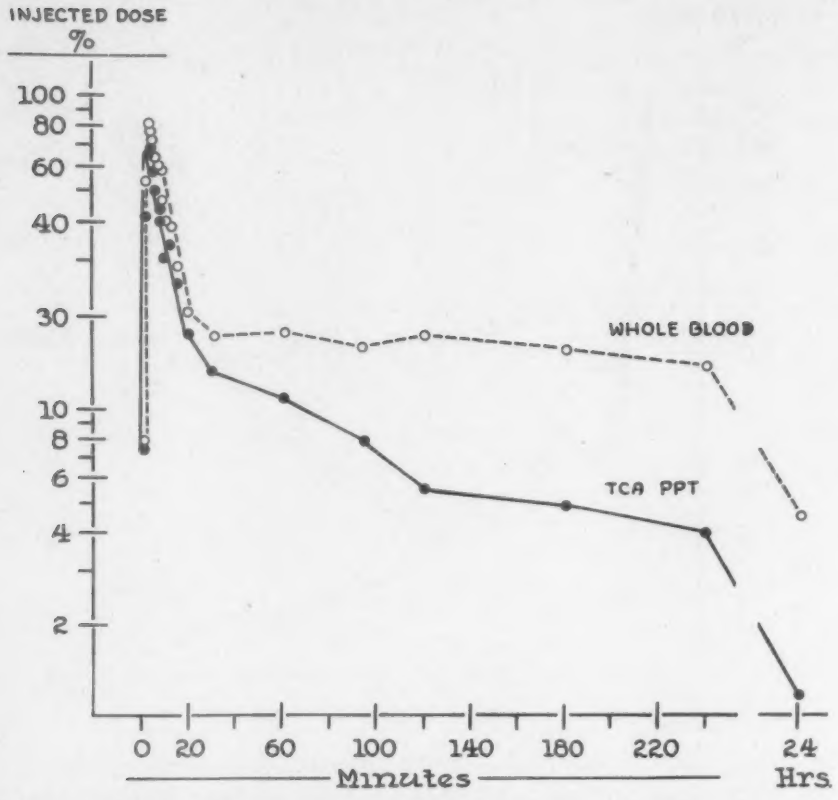

FIG. 4. Case 15. Disappearance of radioactivity from the whole blood and its circulating lipoprotein fraction in a myxedematous subject who had received I^{131}-triolein intravenously.

are not infrequently attended by pyrogenic, vasomotor and allergic reactions as well as other problems associated with the introduction of colloidal material into the blood stream.[13] The stability of these preparations is important clinically since hydrolytic products have been proven capable of hemolyzing the red cells of the subject into whom they are injected. The particle size also plays an important role because the larger particles are removed by the reticuloendothelial system of the lungs and liver at a more rapid rate than the remainder of the mixture and will not be metabolized by the same enzyme systems as the study material. The radioactivity introduced must be homogeneous with the carrier material and sterility must be maintained without hydrolyzing the radioactive substance introduced or its carrier vehicle. Until recent times such emulsions had to be prepared by tedious grinding in a ball-mill apparatus or by recycling the ingredients in a Hydropulse dairy-type homogenizer.[14] Owing to the pioneer efforts of Zilversmit and his co-workers,[15] anhydrous premixes have become available that are capable of forming fine lipid emulsions upon dilution with an aqueous solution.

To assure that the radioactive triolein formed an integral part of the mixture rather than just floating as globules of oil on the surface, the introduced radioactive material was first homogenized with the anhydrous "pre-mix," using a high speed rotor in a manner similar to that described by Weinman, Chaikoff et al.[16] The mixture thus formed was diluted with 5 per cent dextrose in water and re-emulsified again. Sterility was obtained by pressure filtration through fine pore Millipore filters. Stability was controlled by using the material within one hour after preparation. The incidence of adverse reactions was low. Pain in the back developed in one patient but subsided without necessity of interrupting the study; three patients had transient episodes of dizziness.

Significance of I^{131}-Triolein Disappearance Curves: From the curves presented in Figures 1, 3 and 4 it is readily seen that the fatty acids of the administered triglycerides are very rapidly bound to the proteins of the blood since approximately 95 per cent of the whole blood radioactivity is present in the fraction precipitable with trichloroacetic acid by the first minute after injection of the isotopic mixture. The results ob-

TABLE II
Change in Fraction of Whole Blood Activity Bound to Protein (TCA/WB) with Time

Case No.	Time (minutes)												
	10	12	15	20	30	40	60	80	100	120	140	160	180
A. Control Group													
1	94.6	86.0	74.2	58.8	52.0	43.2	29.6	27.7	24.7	23.5	21.0	19.1	18.5
2	81.4	77.2	74.3	52.5	48.0	38.3	27.8	28.2	24.8	24.1	23.2	24.8	23.1
3	94.4	94.2	87.9	...	63.2	48.5	41.0	27.5	18.4	22.0	20.7	20.0	26.4
4	70.3	56.0	50.5	35.0	25.0	21.5	27.9	13.7	12.8	12.0	12.6	10.8	9.7
5	76.7	75.3	66.3	60.2	...	33.7	24.8	22.1	14.5	11.6	12.2	11.2	8.2
6	81.2	75.3	62.3	49.8	39.6	29.3	21.7	21.9	18.5	15.1	16.0	13.3	16.0
7	72.4	65.2	60.9	50.0	37.9	33.3	28.8	26.9	26.7	25.1	24.7	24.5	21.9
8	50.6	...	38.8	...	27.3	...	...	...	...	10.3	...	...	...
9	58.5	44.7	38.8	...	23.6	...	14.7	...	...	14.9	...	...	11.9
Mean	75.6	68.5	61.6	51.1	39.6	35.4	26.8	24.0	20.0	17.6	18.6	17.7	17.0
B. Myocardial Infarction													
10	81.6	...	64.0	42.4	55.2	44.1	18.0	15.8	15.7	12.6	15.6	11.5	10.8
11	74.7	71.0	59.8	53.6	44.8	39.2	24.8	27.9	20.8	18.8	16.9	17.9	15.7
12	75.4	57.6	54.3	41.0	42.7	39.0	30.8	25.5	25.4	24.8	23.2	21.5	19.5
13	63.5	52.9	41.9	35.8	31.9	24.9	29.7	21.3	...	21.8	21.6	19.4	19.2
14	83.6	...	67.8	56.4	45.9	...	31.2	...	...	...	...	...	...
Mean	75.4	60.5	57.6	46.7	44.1	36.8	26.9	22.6	20.6	19.5	19.3	17.6	16.3
C. Myxedema Group													
15	75.8	86.2	88.3	87.6	78.6	...	62.4	...	49.1	32.1	...	...	31.3
16	88.4	84.8	...	78.3	65.5	59.5	39.5	30.6	32.9	28.5	27.7	26.3	...
17	95.2	90.2	86.2	...	63.8	53.2	31.4	28.3	31.7	19.8	20.3	21.6	21.6
Mean	86.5	87.1	87.3	83.0	69.3	56.4	44.4	29.5	37.9	26.8	24.0	24.0	26.5
D. Primary Amyloidosis of Heart													
18	93.6	89.2	89.3	84.9	68.0	61.2	40.9	35.8	31.9	31.6	34.8	28.3	...

tained in this study are similar to those described by McCandless and Zilversmit[12] in the dog utilizing both a synthetic emulsion labeled with I^{131}-triolein and chylomicra labeled in the triglyceride moiety with I^{131}. With their synthetic triolein emulsion there was a very rapid exponential disappearance of I^{131} from the blood stream during the first few minutes with a $T^1/_2$ of approximately three minutes. There was somewhat less radioactive lipid remaining after one hour in their study (1 to 3 per cent of injected dose compared to about 10 per cent in the population studied by us). However, we also found that the ratio of radioactive lipid to whole blood activity at the end of one hour was about 20 to 30 per cent.

The rapid removal of labeled triglyceride from the blood stream in both of these studies with I^{131}-labeled triglyceride is comparable to the results previously reported by Goldman et al.[17] using C^{14}-tripalmitin emulsions where 1 to 3 per cent of the injected dose remained in the dog's plasma at the end of one hour. When McCandless and Zilversmit injected I^{131}-labeled chylomicra instead of the triglyceride emulsion into their animals, the times of disappearance of the radioactivity from the blood stream were somewhat longer but of a similar order of magnitude. When Frederickson et al.[18] infused C^{14}-labeled chylomicra into dogs, they found a $T^1/_2$ of 2.5 to 4.5 minutes during the rapid phase of clearance. The rapid rise of radioactivity into the free fatty

acid (FFA) fraction of the blood with a peak level occurring at six to ten minutes, would help to explain the slowing rate of disappearance of the injected radioactivity during this interval found in our study. The wide deviation of the whole blood activity curve from that of the lipoprotein (TCA) curve would also be readily explained by the peak levels of oxidation of FFA found by Frederickson et al.[18] thirty to seventy minutes after injection of the isotope. During the period of rapid oxidation, deiodination would occur with subsequent release of the inorganic iodide into the blood stream. The secondary rise of both whole blood and circulating lipoprotein activity found in our study can also be explained by recycling of the FFA fraction back into the blood stream.

The $T^1/_2$ found in our data was a little slower than that found by Frederickson and his coworkers[19] in human subjects who had received C^{14} complexed to albumin as FFA intravenously. Their deviations from linearity, however, occurred at the same time as did those in our study. Moreover, the complexities of the curves representing reflux of the radioactive FFA back into the blood stream occurred at the same time intervals.

Since synthetic emulsions may differ in particle size, fat content and nature of the stabilizer, and because certain of the results of previous investigations show tissue distribution and rates of oxidation which differ from the studies employing actual lymph chylomicra,[11] certain authors[20,21] have cast doubt on the interpretation of these studies in terms of normal chylomicron metabolism. There is good evidence, however, that some fat emulsions may represent substrate readily available for caloric purposes[22] and behave similarly to ingested fat.[23]

I^{131}-Triolein Disappearance Curves in Patients with Coronary Artery Disease: Although the absorptive phase has been bypassed, these curves are still a resultant of many complex factors of which rate of transfer of triglyceride from the blood, rate of hydrolysis of triglyceride, rate of utilization of FFA and responsiveness of adipose tissue to the exogenous supply of fat all play important roles.[11] Despite these complexities, the disappearance curves in patients with myocardial infarction are almost identical with those of the control group (Tables I and II). Since previous studies[7] have shown that following oral administration of I^{131}-labeled triolein there are clear cut differences in the rate of appearance and disappearance of the radioactivity from the blood stream, it appears that the prime defect in these disorders may be intimately linked up with absorption of the neutral fat.

I^{131}-Triolein Curves in Patients with Hypothyroidism: In contrast to the population with myocardial infarction, clear cut differences from the control group are observed in the clearance of I^{131}-labeled triglyceride in the myxedematous group. The radioactivity takes longer to reach a maximum in the blood stream and disappears at a much slower rate. Moreover, the fraction of total radioactivity remaining as circulating lipoprotein remains significantly higher. These data would point to both diminished rate of transfer of triglycerides from the blood and impaired oxidation of the fatty acids.

Summary

1. Synthetic emulsions containing I^{131}-triolein were administered intravenously to nine control subjects with no evidence of lipid disease, five patients with myocardial infarction, three with hypothyroidism and one with primary amyloidosis of the heart.

2. No severe toxic reactions were noted.

3. Disappearance curves of radioactivity from the whole blood, the circulating lipoprotein and the ratio of the circulating lipoprotein to whole blood were obtained. These showed a rapid disappearance phase, followed by a slower disappearance phase and evidence of recycling.

4. There was no difference between the control group and the patients with myocardial infarction.

5. The patients with hypothyroidism and the patient with primary amyloidosis showed delayed excretion of the radioactivity from the blood and circulating lipoprotein fraction.

References

1. Thannhauser, S. J. and Stanley, M. M. Serum fat curves following oral administration of I^{131} labeled neutral fat to normal subjects and those with idiopathic hyperlipemia. *Tr. A. Am. Physicians*, 62: 245, 1959.
2. Stanley, M. M. and Thannhauser, S. J. The absorption and disposition of orally administered I^{131} labeled neutral fat in man. *J. Lab & Clin. Med.*, 34: 1634, 1949.
3. Ruffin, J. M., Shingleton, W. W., Baylin, G. J., Hymans, J. C., Isley, J. K., Sanders, A. R. and Sohmer, M. F. I^{131} labeled fat in the study of intestinal absorption. *New England J. Med.*, 255: 594, 1956.
4. Beres, P., Wenger, J. and Kirsner, J. B. The use of I^{131} triolein in the study of absorptive disorders in man. *Gastroenterology*, 32: 1, 1957.

5. Turner, D. A. The absorption, transport and deposition of fat. Application of a new method for the determination of I^{131} lipid activity in dogs and man. Part 1 and 2. *Am. J. Digest Dis.*, (N S) 13: 594, 682, 1958.
6. Berkowitz, D. and Sklaroff, D. The use of radioactive fat in the study of absorption in various disease states. *Arch. Int. Med.*, 100: 951, 1957.
7. Seller, R. H., Brockfeld, J., Sandberg, H. and Bellet, S. The use of I^{131} labeled fat in the study of lipid handling in patients with coronary artery disease. *Am. J. Med.*, 27: 231, 1959.
8. Likoff, W., Berkowitz, D., Woldow, A., Gerson Jacobs, A. and Sklaroff, D. Radioactive fat absorption patterns; their significance in coronary artery atherosclerosis. *Circulation*, 18: 1118, 1958.
9. Berkowitz, D., Sklaroff, D., Woldow, A., Gerson Jacobs, A. and Likoff, W. Blood absorptive patterns of isotopically labelled fat and fatty acid. *Ann. Int. Med.*, 50: 247, 1959.
10. Sandberg, H., Min, B., Feinberg, L. J. and Bellet, S. I^{131} triolein tolerance curves in patients with diabetes mellitus: Their similarity to those in myocardial infarction. *Arch. Int. Med.*, 105: 866, 1960.
11. Frederickson, D. S. and Gordon, R. S., Jr. Transport of fatty acids. *Physiol. Rev.*, 38: 585, 1958.
12. McCandless, E. L. and Zilversmit, D. B. Fate of triglycerides and phospholipids of lymph and artificial fat emulsions; disappearance from the circulation. *Am. J. Physiol.*, 193: 294, 1958.
13. Waddell, W. R., Geyer, R. P., Olsen, F. R., Andrus, S. R. and Stare, F. J. Clinical experience with intravenous infusion of emulsified fat. *J. Lab. & Clin. Med.*, 45: 697, 1955.
14. Geyer, R. P., Olsen, F. R., Andrus, S. B., Waddell, W. R. and Stare, F. J. The preparation of fat emulsions for intravenous alimentation. *J. Am. Oil. Chem. Soc.*, 32: 365, 1955.
15. Zilversmit, D. B., Salky, N. K., Trumbull, M. L. and McCandless, E. L. The preparation and use of anhydrous fat emulsions for intravenous feeding and metabolic experiments. *J. Lab. & Clin. Med.*, 48: 386, 1956.
16. Weinman, E. O., Chaikoff, I. L., Dauben, W. G., Gee, M., and Entenman, C. Relative rates of conversion of the various carbon atoms of palmitic acid to carbon dioxide by the intact rat. *J. Biol. Chem.*, 184: 735, 1950.
17. Goldman, D. S., Chaikoff, I. L., Reinhardt, W. O., Entenman, C. and Dauben, W. G. Site of formation of plasma phospholipides studied with C^{14} labeled palmitic acid. *J. Biol. Chem.*, 184: 727, 1950.
18. Frederickson, D. S., McCollester, D. L. and Ono, K. The role of unesterified fatty acid transport in chylomicron metabolism. *J. Clin. Invest.*, 37: 1333, 1958.
19. Frederickson, D. S., Gordon, R. S., Ono, K. and Cherkes, A. The metabolism of albumin-bound C^{14} labeled unesterified fatty acids in normal human subjects. *J. Clin. Invest.*, 37: 1504, 1958.
20. Morris, B. and Courtice, F. C. The origin of chylomicrons in the cervical and hepatic lymph. *Quart. J. Physiol.*, 41: 341, 1956.
21. Murray, R. G. and Freeman, S. The morphologic distribution of intravenously injected fatty chyle and artificial emulsions in rats and dogs. *J. Lab. & Clin. Med.*, 38: 56, 1951.
22. Geyer, R. P., Chipman, J. and Stare, F. J. Oxidation in vivo of emulsified radioactive trilaurin administered intravenously. *J. Biol. Chem.*, 176: 1469, 1948.
23. Waddell, W. R. and Geyer, R. P. Effect of insulin on clearance of emulsified fat from the blood in depancreatized dogs. *Proc. Soc. Exper. Biol. & Med.*, 96: 251, 1957.

Blood Pressure Measurements In Obese Persons

Comparison of Intra-arterial and Auscultatory Measurements*

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IN RECENT YEARS, the relationship of obesity and arterial hypertension has received considerable attention. It is widely accepted that arterial hypertension is more common among the obese than among the lean.[1–4] A technical difficulty in measuring the blood pressure of obese persons has been recognized; conventional sphygmomanometry may give falsely high readings when the arm is big[5] and may, on occasion, result in an unwarranted diagnosis of hypertension. Earlier investigations of this problem, consisting of comparisons between direct intra-arterial measurements and indirect measurements by the cuff method, either dealt with too small a number of subjects or used technics which appear open to criticism (e.g., measurements not simultaneous or not made in the same arm). We, therefore, decided to investigate the problem with modern electronic equipment and a larger number of subjects.

MATERIAL AND METHOD

One hundred subjects were used for this study. They were drawn from the wards and the outpatient department of a large general hospital and were suffering from the various diseases encountered in the hospital population. Patients exhibiting atrial fibrillation were excluded.

The subjects varied in age from sixteen to eighty-four years (average, fifty-six years). Only three were twenty-one years old or less; seven were seventy years old or more. Forty-four were men, fifty-six were women. Seventy patients were hypertensive, thirty were normotensive.† Sixty-one patients were obese, thirty-nine were nonobese. The Ponderal Index W/H, weight per inch of height, was used to appraise body bulk and to delimit obesity. A Ponderal Index of 2.817 was arbitrarily chosen as the dividing line. All subjects with a Ponderal Index higher than 2.817 were classified as obese. The obese group included fifty hypertensive subjects and eleven normotensive subjects. The nonobese group included nineteen hypertensive subjects and twenty normotensive subjects.

Simultaneous direct and indirect arterial blood pressure measurements were made in all 100 subjects. The brachial artery was used for the intra-arterial measurements, a Sanborn Electromanometer was used for measuring the pressures and a direct writing electrocardiograph, Sanborn Twin-Viso, was used for recording them. Our technic has been described in detail elsewhere.[6] The indirect blood pressure measurement (auscultatory method) was made on the same arm by means of a commercial sphygmomanometer (Baumanometer, wall type, cuff measurement 13 by 20 cm., with tapered cotton sleeve). The highest and lowest systolic and diastolic pressures recorded on each tracing were compared to the final blood pressure reading obtained with the cuff method.

RESULTS

Systolic Pressure: Table I is a summary of all direct and indirect blood pressure measurements. The subjects are arranged according to their Ponderal Indices. The first thirty-nine have a Ponderal Index ranging from 1.582 to 2.776; they constitute the nonobese group. The remaining sixty-one subjects are obese. Their Ponderal Indices range from 2.818 to 5.625. Discrepancies of varying magnitude are shown to occur in both groups. Tables II and III summarize the comparisons of systolic pres-

† We regarded a person as hypertensive when his systolic blood pressure, determined by intra-arterial measurement, exceeded 150 and his diastolic pressure, 90 mm. Hg.

* From the Department of Medicine, New York Medical College, Metropolitan Medical Center, New York, New York.

TABLE I
Summary of All Blood Pressure Determinations: Indirect and Direct Intra-Arterial

Case No.	Age	Weight (lb.)	Height	Ponderal Index (W/H)	Blood Pressures (mm. Hg)						Higher Reading	
					Indirect Method (Cuff)		Direct Intra-arterial Method					
							Highest Reading		Lowest Reading			
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
1	46	106	5′7	1.582	98	56	95	52	93	49	Cuff	Cuff
2	39	103	5′3″	1.634	96	68	93	47	92	49	Cuff	Cuff
3	21	108	5′5½″	1.648	93	73	90	67	88	54	Cuff	Cuff
4	28	105	5′1″	1.721	108	70	105	65	95	60	Cuff	Cuff
5	57	114	5′4″	1.781	104	68	105	62	95	57	Direct	Cuff
6	53	127	5′10½″	1.801	126	78	118	63	112	58	Cuff	Cuff
7	77	117	5′4	1.828	227	76	233	78	230	78	Direct	Direct
8	21	114	5′2″	1.838	128	71	124	85	120	83	Cuff	Direct
9	44	116½	5′2″	1.878	133	70	134	70	130	90	Direct	Same
10	37	132	5′10″	1.885	122	90	123	77	117	74	Direct	Cuff
11	16	126	5′6″	1.916	127	73	165	78	153	78	Direct	Direct
12	40	116	4′11½″	1.949	133	78	132	84	122	84	Cuff	Direct
13	84	140	5′9½″	2.015	152	92	187	83	172	80	Direct	Cuff
14	57	134	5′6″	2.030	130	80	146	74	140	73	Direct	Cuff
15	60	140	5′8″	2.058	172	72	152	63	145	66	Cuff	Cuff
16	65	134	5′5″	2.065	210	100	240	105	228	95	Direct	Direct
17	56	135	5′5″	2.076	130	80	132	72	118	72	Direct	Cuff
18	71	142	5′6″	2.151	162	104	194	103	177	117	Direct	Cuff
19	80	140	5′5″	2.153	252	60	255	60	240	50	Direct	Same
20	45	135	5′2½″	2.160	130	80	130	78	120	72	Same	Cuff
21	77	137	5′3″	2.174	125	80	130	69	123	70	Direct	Cuff
22	58	124	4′8½″	2.194	188	90	182	83	176	83	Cuff	Cuff
23	51	142	5′4½″	2.201	164	58	155	50	145	54	Cuff	Cuff
24	63	148	5′7″	2.208	146	62	173	76	168	79	Direct	Direct
25	70	136	5′1½″	2.211	262	108	248	101	242	101	Cuff	Cuff
26	48	133	5′0″	2.216	245	135	270	130	225	118	Direct	Cuff
27	65	145	5′3″	2.301	260	100	260	100	245	95	Same	Same
28	82	152	5′5½″	2.320	144	86	155	60	149	68	Direct	Cuff
29	60	137	4′9½″	2.382	260	109	223	87	215	85	Cuff	Cuff
30	69	159	5′6″	2.416	118	68	122	58	112	65	Direct	Cuff
31	63	162	5′6″	2.454	117	73	112	64	105	63	Cuff	Cuff
32	64	159	5′1″	2.606	160	94	163	78	150	68	Direct	Cuff
33	61	174	5′5½″	2.656	152	74	158	72	150	69	Direct	Cuff
34	56	187	5′9″	2.710	118	70	132	70	115	70	Direct	Same
35	55	185	5′8″	2.720	126	74	138	70	123	70	Direct	Cuff
36	67	188	5′9″	2.724	170	68	179	66	162	71	Direct	Direct
37	60	169	5′1″	2.759	123	68	118	65	111	58	Cuff	Cuff
38	69	184	5′6½″	2.766	161	96	179	97	175	92	Direct	Direct
39	74	193	5′9½″	2.776	142	78	182	82	158	83	Direct	Direct
40	50	186	5′6″	2.818	110	72	118	72	105	67	Direct	Same
41	59	181	5′4″	2.828	166	104	151	96	146	95	Cuff	Cuff
42	74	191	5′7½″	2.829	189	62	165	65	162	65	Cuff	Direct
43	65	162	4′9″	2.842	196	60	201	55	176	62	Direct	Cuff
44	50	185	5′4″	2.872	200	130	198	100	170	90	Cuff	Cuff
45	50	171	4′11½″	2.873	202	100	190	88	186	89	Cuff	Cuff
46	38	198½	5′9″	2.876	178	100	150	85	139	84	Cuff	Cuff
47	68	201½	5′10″	2.878	111	71	97	63	90	59	Cuff	Cuff
48	64	190	5′6″	2.878	131	76	153	83	145	67	Direct	Direct
49	67	190	5′6″	2.878	198	72	215	70	205	70	Direct	Cuff
50	48	183	4′9½″	2.950	235	120	241	128	222	123	Direct	Direct

TABLE 1 (*Continued*)

Case No.	Age	Weight (lb.)	Height	Ponderal Index (W/H)	Blood Pressures (mm. Hg)						Higher Reading	
					Indirect Method (Cuff)		Direct Intra-arterial Method					
							Highest Reading		Lowest Reading			
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
51	49	183	4′9½″	2.950	210	114	212	108	209	107	Direct	Cuff
52	60	198	5′7″	2.955	192	132	200	125	192	120	Direct	Cuff
53	54	190	5′4″	2.968	103	72	120	58	112	55	Direct	Cuff
54	46	196	5′6″	2.969	150	75	159	83	151	82	Direct	Direct
55	57	200	5′7″	2.985	166	110	168	112	159	106	Direct	Direct
56	69	200	5′7″	2.985	176	94	170	98	166	69	Cuff	Direct
57	50	212	5′10″	3.028	140	78	143	72	132	70	Direct	Cuff
58	63	200	5′6″	3.030	126	62	121	54	116	55	Cuff	Cuff
59	51	176	4′10″	3.034	182	90	195	100	185	95	Direct	Direct
60	65	213	5′10″	3.042	142	60	124	56	120	56	Cuff	Cuff
61	48	200	5′4″	3.125	160	90	170	85	142	88	Direct	Cuff
62	66	217	5′9″	3.144	147	40	152	43	150	45	Direct	Direct
63	69	192½	5′1″	3.155	185	95	185	95	180	85	Same	Same
64	65	193	5′1″	3.163	206	130	195	113	181	110	Cuff	Cuff
65	49	197	5′2″	3.177	202	103	206	97	201	97	Direct	Cuff
66	68	183	4′9½″	3.182	128	90	150	68	135	64	Direct	Cuff
67	56	202	5′2″	3.258	193	94	174	68	165	75	Cuff	Cuff
68	51	207	5′2½″	3.312	186	108	200	122	190	120	Direct	Direct
69	44	220	5′5″	3.384	200	140	180	140	170	136	Cuff	Same
70	36	220	5′5″	3.384	148	111	154	97	143	95	Direct	Cuff
71	60	210	5′2″	3.387	141	50	159	65	138	57	Direct	Direct
72	60	225	5′½″	3.488	222	126	223	110	214	111	Direct	Cuff
73	59	232	5′6″	3.515	122	88	126	80	120	80	Direct	Cuff
74	55	239	5′7″	3.567	192	115	198	110	195	110	Direct	Cuff
75	53	226	5′3″	3.587	210	110	220	115	210	105	Direct	Direct
76	59	216	5′0″	3.600	154	90	180	88	168	83	Direct	Cuff
77	57	224	5′2″	3.612	158	104	176	120	164	119	Direct	Direct
78	73	212	4′10½″	3.623	146	92	156	101	136	91	Direct	Direct
79	62	227	5′2″	3.632	168	99	173	120	152	109	Direct	Direct
80	50	221	4′11″	3.745	254	142	242	123	229	117	Cuff	Cuff
81	45	244	5′5″	3.760	164	80	173	82	162	78	Direct	Direct
82	34	248	5′5½″	3.786	133	77	137	73	122	73	Direct	Cuff
83	57	231	5′1″	3.786	120	64	131	82	120	75	Direct	Direct
84	58	238	5′0″	3.966	188	108	180	96	170	95	Cuff	Cuff
85	27	265	5′5″	4.076	126	84	118	78	116	81	Cuff	Cuff
86	65	265	5′5″	4.076	125	76	129	78	119	74	Direct	Direct
87	51	264	5′3″	4.190	160	90	176	83	166	83	Direct	Cuff
88	36	290	5′9″	4.202	184	123	201	122	185	111	Direct	Cuff
89	71	237	4′8″	4.232	188	80	205	87	190	82	Direct	Direct
90	65	255	5′0″	4.250	238	130	230	118	218	124	Cuff	Cuff
91	59	274	5′4″	4.281	170	92	152	95	138	88	Cuff	Direct
92	38	270	5′3″	4.285	156	102	159	94	154	97	Direct	Cuff
93	62	275	5′1″	4.524	190	90	171	83	137	86	Cuff	Cuff
94	63	275	5′1″	4.524	196	94	152	66	134	61	Cuff	Cuff
95	48	287	5′3″	4.555	262	138	212	110	200	95	Cuff	Cuff
96	38	278	4′11½″	4.672	178	100	150	85	139	84	Cuff	Cuff
97	48	276	4′11″	4.677	236	150	208	123	205	125	Cuff	Cuff
98	58	315	5′1½″	5.121	141	88	135	67	120	66	Cuff	Cuff
99	49	350	5′7″	5.223	250	150	199	115	178	104	Cuff	Cuff
100	58	391	5′9½″	5.625	159	116	162	91	140	87	Direct	Cuff

TABLE II

Systolic Blood Pressure Readings—Comparison of Direct and Indirect Measurements

Reading	Comparison			Total Cases
	Direct Reading Higher	Indirect Reading Higher	Readings Identical	
A. Sixty-One Obese Persons				
Actual readings compared	36	24	1	61
Differences of 1 or 2 mm. disregarded	33	23	5	61
B. Thirty-Nine Nonobese Persons				
Actual readings compared	23	14	2	39
Differences of 1 or 2 mm. disregarded	19	13	7	39

TABLE III

Systolic Blood Pressure Readings—Extent of Discrepancies between Direct and Indirect Measurements

Reading	Discrepancy						Total Cases
	1–2 mm.	3–5 mm.	6–10 mm.	11–20 mm.	21–30 mm.	Over 30 mm.	
A. Sixty-One Obese Persons							
Direct measurement higher	3	10	11	9	3	0	36
Indirect measurement higher	1	1	5	10	4	3	24
Readings identical	...	...	...	...	...	...	1
B. Thirty-Nine Nonobese Persons							
Direct measurement higher	1	7	3	2	0	1	14
Indirect measurement higher	4	4	3	5	3	4	23
Readings identical	...	...	...	...	...	...	2

TABLE IV

Diastolic Blood Pressure Readings—Comparison of Direct and Indirect Measurements

Reading	Comparison			Total Cases
	Direct Reading Higher	Indirect Reading Higher	Readings Identical	
A. Sixty-One Obese Persons				
Actual readings compared	19	39	3	61
Differences of 1 or 2 mm. disregarded	16	36	9	61
B. Thirty-Nine Nonobese Persons				
Actual readings compared	9	26	4	39
Differences of 1 or 2 mm. disregarded	7	23	9	39

sure in the obese and nonobese persons. Table II shows the frequency of the discrepancies, Table III their magnitude. Most discrepancies in the obese persons were minor; in three subjects, however, the indirect method grossly underestimated systolic pressure by 22 to 26 mm., and in seven subjects the indirect method grossly overestimated systolic pressure by 24, 28, 28, 28, 44, 50 and 51 mm., respectively. In the nonobese persons, too, most of the discrepancies were minor. However, gross overestimation of systolic pressure also occasionally occurred among these lean persons, in one instance amounting to 37 mm. Underestimation of systolic pressure of lean persons by the indirect method was more common and more marked, amounting to as much as 25 to 40 mm.

Diastolic Pressure: In both groups systolic pressure was underestimated by the indirect method more often that it was overestimated. The opposite was found when diastolic pressures were compared. The indirect method overestimated diastolic pressure in the majority of all cases, obese and nonobese. Tables IV and V summarize the comparisons of diastolic pressure in the obese and nonobese subjects, Table IV showing the frequency of the discrepancies, Table V their magnitude. Among the obese subjects, most of the discrepancies in diastolic pressure were again minor. Gross underestimation occurred only twice (by 16 and 18 mm.) and gross overestimation much more frequently, twelve times (by 16 to 35 mm.) In the nonobese group gross underestimation of diastolic pressure did not occur; gross overestimation occurred four times, amounting to 16 to 22 mm.

Extreme Obesity vs. Leanness: The similarity of findings in both groups at first seemed to indicate that obesity has little effect on the measurement of blood pressure. Very different re-

TABLE V

Diastolic Blood Pressure Readings—Extent of Discrepancies between Direct and Indirect Measurements

Reading	Discrepancy						Total Cases
	1–2 mm.	3–5 mm.	6–10 mm.	11–15 mm.	16–20 mm.	Over 20 mm.	
A. Sixty-One Obese Persons							
Direct measurement higher	3	5	6	3	2	0	19
Indirect measurement higher	3	5	11	8	4	8	39
Readings identical	...	...	...	...	...	...	3
B. Thirty-Nine Nonobese Persons							
Direct measurement higher	2	4	1	2	0	0	9
Indirect measurement higher	3	6	10	3	3	1	26
Readings identical	...	...	...	...	...	...	4

sults, however, were obtained when extreme obesity was contrasted with marked leanness. Table VI limits the comparisons to the ten stoutest subjects (Ponderal Index 4.250 to 5.625) and the ten leanest subjects (Ponderal Index 1.582 to 1.885). In eight of the ten very obese subjects, the indirect method overestimated the systolic pressure. The greatest discrepancies of the whole series were encountered in this small group. Diastolic pressure in these very stout subjects also was overestimated in nine out of ten cases, and by a substantial number of points. These findings were in striking contrast to those in the ten leanest subjects. Here no significant overestimation or underestimation of either systolic or diastolic pressure occurred.

Lastly, we selected from both groups the twelve cases which demonstrated the greatest overestimation of systolic blood pressure by the indirect method (Table VII). The discrepancies ranged from 18 to 51 mm. Ten of the twelve subjects were obese and the five greatest discrepancies of the entire series occurred in extremely obese persons. Here the effect of obesity, falsely high readings, is most apparent.

COMMENT

Effect of Obesity on Blood Pressure: From the outset two separate problems presented themselves; (1) the effect of obesity on blood pressure; (2) errors of clinical blood pressure measurements caused by the large arms of obese persons. As to the first problem, any investigation into the effect of obesity on blood pressure obviously has to find a true measure of obesity first. Measurement of total body fatness can probably furnish the best measure of obesity, but the methods are not yet practicable.[8] Another method of assessment is to measure the circumference of the subject's arm. A recent study by Whyte,[1] however, clearly shows that circumference of the arm and blood pressure are unrelated. Blood pressure, measured in the ordinary way, was noted to be higher in subjects with larger arms, but the association lost significance when the influence of other factors such as age, weight and height was excluded.

TABLE VI

Ten Stoutest and Ten Leanest Subjects—Comparison of Direct and Indirect Blood Pressure Measurements

Blood Pressure Measurement	10 Stoutest Subjects		10 Leanest Subjects		Readings Identical
	Direct Measurement Higher	Indirect Measurement Higher	Direct Measurement Higher	Indirect Measurement Higher	
Systolic pressure	2 cases (each by 3 mm.)	8 cases (by 6, 18, 19, 28, 28, 44, 50 and 51 mm., respectively)	4 cases (by 1, 1, 1 and 6 mm., respectively)	6 cases (by 3, 3, 3, 3, 4 and 8 mm., respectively)	0
Diastolic pressure	1 case (by 3 mm.)	9 cases (by 4, 5, 15, 15, 21, 25, 28, 28 and 35 mm., respectively)	2 cases (by 2 and 6 mm., respectively)	7 cases (by 4, 5, 6, 6, 13, 15 and 19 mm., respectively)	1

TABLE VII
Twelve Greatest Overestimations of Systolic Blood Pressure by the Indirect Method

Case No.	Weight (lb.)	Height	Ponderal Index (W/H)	Systolic Pressure (mm. Hg)		
				Direct Measurement	Indirect Measurement	Systolic Pressure Higher (mm.)
60	213	5′10″	3.042	124/56	142/60	18
91	274	5′4″	4.281	152/95	170/92	18
67	202	5′2″	3.258	174/68	193/94	19
15	140	5′8″	2.058	152/63	172/72	20
69	220	5′5″	3.384	180/140	200/140	20
42	191	5′7½″	2.829	165/65	189/62	24
96	278	4′11½″	4.672	150/85	178/100	28
97	276	4′11″	4.677	208/123	236/150	28
29	137	4′9″	2.382	223/87	260/109	37
94	275	5′1″	4.524	152/66	196/94	44
95	287	5′3″	4.555	212/110	262/138	50
99	350	5′7″	5.223	199/115	250/150	51

NOTE: Ten subjects were obese; two subjects were nonobese.

Still another way of judging obesity is by estimating the amount of subcutaneous fat. This is done by pinching up skin folds and measuring their thickness. Whyte[1] found that obesity thus judged also has no apparent influence on blood pressure execpt as it affects the total body weight. Whyte noted that the composition of a person's excess weight is immaterial; it is the over-all bulk which counts, be it muscle or fat. In our own investigation we, therefore, dispensed with measurements of circumference of the arm and estimations of subcutaneous fat. Our task was to measure over-all bulk. Weight alone is obviously not very informative about the bulk of the body, the bulk being dependent on height as well as on other dimensions of the body. None of the available methods of measuring bulk is entirely reliable. The Ponderal Index W/H, weight per inch of height, however, is in our opinion the simplest and best comparative measure of body bulk and was employed in the present study.

It has been shown by other investigators that obesity is statistically associated with blood pressure levels above average, and that weight reduction by dieting may produce considerable falls of arterial pressure when it is initially high.[10,15] Our series is relatively small and our hospital patients do not represent a true cross section of the entire population. Our figures, 82 per cent hypertensive subjects in the obese groups, 49 per cent hypertensive subjects in the nonobese group, therefore, have no statistical significance although they effectively demonstrate the relationship between obesity and hypertension. This relationship is still better shown if only the leanest and most stout are compared. Of the ten leanest patients in our group only one was hypertensive; nine were normotensive. Of the ten stoutest patients, on the other hand, nine were hypertensive and only one was normotensive.

Errors in Blood Pressure Measurements in Obese Persons: The possible errors of clinical blood pressure measurement in obese persons are, of course, an entirely different problem. These errors have been widely publicized.[17–19] Several authors[5,17,18] have reported falsely high readings in the obese arm and have given the impression that an unwarranted diagnosis of hypertension is a common occurrence. This problem seemed to us of enough importance to require further investigation. Does the obese arm regularly cause falsely high readings, or, if not, how common are they? What is the extent of these errors, and are they proportionate to the degree of obesity? Are many obese persons falsely classified as hypertensives? These were the questions to which we sought the answers.

We first reviewed the earlier investigations of the problem. Ragan and Bordley[5] were the first to demonstrate the error incurred by taking the blood pressure in obese persons. Using fifty-one subjects, they compared blood pressure measurements made by the auscultatory method in the right arm and simultaneous direct intra-arterial measurements, made with a Hamilton manometer, in the left arm. They found that in subjects with large arms the auscultatory readings were usually too high, the errors amounting to between 10 and 20 mm. Hg. Trout, Bertrand and Williams[18] made comparisons on six extremely obese persons and eight nonobese persons (weights not stated). Overestimation of systolic pressure by the indirect method, varying from 32 to 102 mm. Hg, occurred in all six obese persons; in the nonobese persons there was a fair degree of agreement between the two methods. Observations made by Irvin, quoted by Smirk,[4] on eight patients with unequal arms showed slight differences between the two on numerous repetitions, the higher reading being obtained on the arm with the larger circumference. Smirk[4] states: "If an arm is artificially thickened by wrapping around it various materials such as cloth, cotton, wool, sponge rubber and meat from the butcher, it is found that these materials have different effects upon the estimated blood pressure. Cloth and meat of a rather compact

consistency had very little effect upon the estimated blood pressure, whereas cotton, wool and sponge rubber increased the estimated blood pressure. Apparently some materials when interposed between the sphygmomanometer cuff and the artery spread the pressure over a wider area so that, in fact, the pressure upon the outside of the artery is less than the pressure within the cuff. Hence the blood pressure is overestimated. The estimated pressure can be brought back to a pressure nearer to that obtained under standard conditions if the cuff is widened." This explanation of the falsely high readings is plausible and should be accepted without qualification. Pickering, Roberts and Sowry[20] reviewed the comparisons reported by Ragan and Bordley[5] and published a list of adjustments for arm circumference to be made to auscultatory pressure. The subtractions to be made from systolic pressure readings in stout arms range from 5 to 25 mm. and those from diastolic readings also from 5 to 25 mm. These authors admit that variations in circumference of the arm do not account for more than a quarter of the differences between direct and indirect readings and doubt the usefulness of applying a correction for arm circumference to an individual reading.

Our own findings lead us to the same conclusion. Besides, marked overestimation of blood pressure by the auscultatory method, in our series, was not at all limited to obese subjects, but occurred in lean persons also. Most noteworthy, however, is our finding of falsely high readings in eight out of ten extremely obese persons. The overestimations ranged from 6 to 51 mm. and were greater than the general range of 10 to 30 mm. reported in the literature.[5,17] Only Trout and associates[18] found discrepancies greater than ours; they ranged from 32 to 102 mm. Hg, with the two greatest, 80 and 102 mm., occurring in the two stoutest arms.

The accuracy of clinical blood pressure measurement in general depends on many factors such as age of the subject, height of true blood pressure, rigidity of arterial wall, contour of pulse wave,[22] and sphygmomanometric technic.[6] Obesity is but one such factor and only in extremely stout subjects can it become decisive. It is the large size of the arm which is responsible for the error. In such persons we found that the difficulty of applying the cuff also plays a part. Often it is difficult to wrap the cotton sleeve evenly around the big arm; not infrequently the sleeve is too short and part of the cuff balloons out when it is inflated. After readjusting the sleeve, markedly different readings were obtained. Attempts to lengthen the sleeve by adding a bandage caused even greater errors.

We always bear in mind the possibility of falsely high readings when dealing with extremely stout persons and are, therefore, not likely to make an unwarranted diagnosis of hypertension. Moreover, most of these very obese persons are true hypertensive subjects anyhow, as shown by intra-arterial measurement; there is little danger of falsely classifying them as hypertensive subjects. In the rare cases in which there is doubt, intra-arterial measurement should be taken.

The large size of the arm, on the other hand, does not always cause falsely high readings. This was nicely shown by the stoutest subject of our entire series, a woman weighing 391 pounds. Her systolic pressure was *underestimated* by the auscultatory method!

Summary

1. Simultaneous direct intra-arterial blood pressure measurements and indirect measurements with the auscultatory method were made in 100 subjects. The subjects were grouped according to their Ponderal Index W/H, weight per inch of height. Sixty-one subjects were obese, thirty-nine were nonobese.

2. Nine out of the ten stoutest subjects were hypertensive, whereas only one of the ten leanest subjects was hypertensive.

3. The indirect method generally underestimates systolic and overestimates diastolic pressure. This holds for lean persons as well as for moderately obese persons.

4. The discrepancies between the direct and indirect methods were usually minor among the lean and the moderately obese subjects and went in both directions. Falsely high blood pressure readings in lean and moderately obese persons are not common.

5. In extremely obese persons the indirect method is subject to considerable error. In eight out of ten such persons the systolic pressure was overestimated, and in nine out of ten such persons the diastolic pressure was overestimated.

6. Overestimation of systolic pressure in very obese persons can be much greater than was heretofore known; it amounted to 44, 50 and 51 mm. in three of our stoutest subjects.

7. Falsely high readings in extremely obese subjects are caused by the large size of their arms. If this possibility is borne in mind, an unwarranted diagnosis of hypertension is not likely to be made. In dubious cases, intra-arterial measurement should be resorted to.

8. Many factors other than arm size may cause inaccuracies of the indirect method, and the large arm does not regularly cause falsely high readings. It is not feasible to apply a correction to an individual reading.

References

1. Whyte, H. M. Blood pressure and obesity. *Circulation*, 19: 511, 1959.
2. Whyte, H. M., Graham, J. A. D. and de Wolfe, M. S. Body fat, blood pressure, and serum cholesterol of Australian men. *Australasian Ann. Med.*, 7: 328, 1958.
3. Whyte, H. M. Body fat and blood pressure of natives in New Guinea. *Australasian Ann. Med.*, 7: 36, 1958.
4. Smirk, F. H. High Arterial Blood Pressure, p. 7. Springfield, Illinois, 1957. Charles C Thomas.
5. Ragan, C. and Bordley, J., iii. The accuracy of clinical measurements of arterial blood pressure. *Bull. Johns Hopkins Hosp.*, 69: 504, 1941.
6. Berliner, K., Fujiy, H., Lee, D. H., Yildiz, M. and Garnier, B. The accuracy of blood pressure determinations. A comparison of direct and indirect measurements. *Cardiologia*, 37: 118, 1960.
7. Bordley, J., iii, Connor, C. A., Hamilton, W. F., Kerr, W. J. and Wiggers, C. J. Recommendations for human blood pressure determinations by sphygmomanometers. *Circulation*, 4: 503, 1951.
8. Keys, A. and Brozek, J. Body fat in adult man. *Physiol. Rev.*, 33: 245, 1953.
9. Dublin, L. J. Relation of obesity to longevity. *New England J. Med.*, 248: 971, 1953.
10. Adlersberg, D., Coler, A. R. and Laval, J. Effect of weight reduction on course of arterial hypertension. *J. Mt. Sinai Hosp.*, 12: 984, 1946.
11. Nuzum, F. R. and Elliot, A. H. An analysis of 500 instances of arterial hypertension. *Am. J. M. Sc.*, 181: 630, 1931.
12. Robinson, S. C., Bruces, M. and Mass, J. Hypertension and obesity. *J. Lab. & Clin. Med.*, 25: 807, 1940.
13. Terry, A. H., Jr. Obesity and hypertension. *J. A. M. A.*, 81: 1283, 1923.
14. Preble, W. E. Obesity: observations in one thousand cases. *Boston Med. Surg. J.*, 188: 617, 1923.
15. Fletcher, A. P. The effect of weight reduction upon the blood pressure of obese hypertensive women. *Quart. J. Med.*, 23: 331, 1954.
16. Boe, J., Hummerfelt, S. and Wedervang, F. The blood pressure in a population. *Acta med. scandinav., suppl.*, 321, 1957.
17. Perera, G. A. Primary hypertension. *Circulation*, 13: 321, 1956.
18. Trout, K. W., Bertrand, C. A. and Williams, M. H. Measurement of blood pressure in obese persons. *J. A. M. A.*, 162: 970, 1956.
19. Pickering, G. W. High blood pressure, p. 20. New York, 1955. Grune & Stratton.
20. Pickering, G. W., Roberts, J. A. F. and Sowry, G. S. C. The effect of correcting for arm circumference on the growth rate of arterial pressure with age. *Clin. Sc.*, 13: 267, 1954.
21. Lachmann, H. Abhaengigkeit der Blucdruckhoehe von der Haerte der Manschette. *Deutsches Gesundheitswesen*, 13: 59, 1958.
22. Thompson, A. E. and Doupe, J. Causes of error in auscultatory blood pressure measurements. *Rev. canadienne biologie*, 8: 337, 1949.

Duration of Arterial Sounds*

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ARTERIAL sounds change in intensity as the cuff pressure falls during the indirect measurement of the blood pressure.[1] The intensity of the sounds has been related to the flow of blood into the extremity.[2] Thus, the sounds are faint when the flow into the extremity is diminished, as by arteriolar constriction or after application of a tourniquet; they become quite loud when the arterioles are dilated. The present study was undertaken to obtain quantitative data on the durations of these vibrations in relation to maneuvers which modify blood flow to the extremity.

METHODS

Arterial sounds were recorded on forty-five subjects, including employees and patients of the Chronic Disease Research Institute.[3] A standard blood pressure cuff, measuring 15 cm. wide, placed on the upper limb of the supine subject, was inflated to pressures higher than the systolic level. The cuff pressure was then allowed to fall steadily at a rate of 2 or 3 mm. Hg per second. Vibrations at the antecubital fossa were recorded by means of a crystal microphone using a constant level of amplification on a Cambridge phonocardiograph. Lead II of the electrocardiogram was recorded simultaneously as a reference tracing. Standardization impulses introduced into the electrocardiogram at each 5 mm. Hg fall of cuff pressure provided a basis for determining the cuff pressure level of each beat.

Control recordings were made with the subject at rest. Arteriolar dilatation was induced in the forearm by inflating the cuff to values above systolic, following which the subject clenched his fist twenty times. The sounds were then recorded as the cuff pressure fell. After a rest period, blood flow in the arm was diminished by application of a tourniquet to the forearm and a third recording was made.

The duration of arterial sounds was measured from the onset of these recorded oscillations until the deviations from the baseline were less than 2 mm.

RESULTS

The effects of the experimental maneuvers on the durations of arterial sounds are illustrated in Figures 1 and 2. The durations of the sounds are recorded at the right of each strip. The effects of tourniquet and exercise were essentially the same in normal subjects and in patients with heart disease.

Two separate components of the sounds contribute to the intensity. These include a transient "snap" at onset which has high pitch and amplitude, followed by a more or less persistent "rumble" of lower pitch. Optical recordings clearly differentiate these two components.[4,5]

NORMAL SUBJECTS

In all twenty normal subjects tested, the durations of arterial sounds increased as the cuff pressure fell from systolic until the greatest duration was recorded, about 20 mm. Hg below systolic pressure (Fig. 1). The durations of the sounds then decreased as the cuff pressure continued to fall until only the snapping onset sound remained at about 40 mm. Hg below systolic levels. The snapping sounds then became muffled. The diastolic value was considered to be the cuff pressure level at which the sounds became inaudible.

Tourniquet: Application of a tourniquet to the forearm markedly diminished the duration and intensity of all the arterial sounds. The general reduction in the sounds made it difficult to select a level of maximum duration.

Vasodilatation: Arteriolar dilatation induced by clenching the fist twenty times resulted in every instance in a marked increase in the amplitude of the snapping sounds and in duration of the rumbling sounds. In these experiments the greatest duration of the sounds

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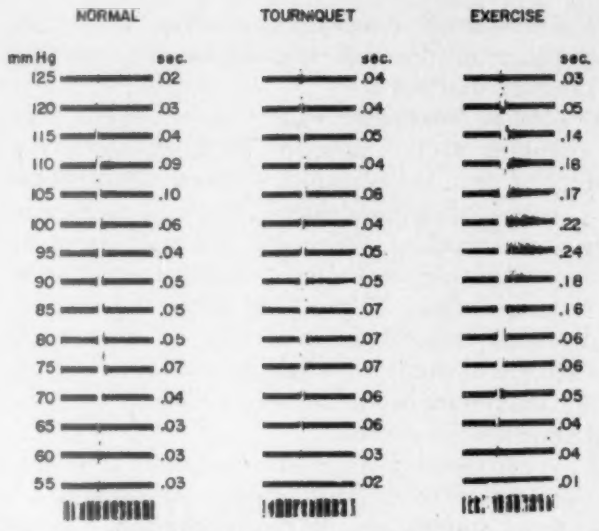

FIG. 1. *Arterial sounds on a normal subject.* The cuttings have been aligned so that the duration of the sounds may be compared. *Normal* represents the sounds recorded at rest. *Tourniquet* represents sounds after blood flow into the forearm was diminished by a cuff on the forearm. *Exercise* represents the sounds after the induction of a reactive vasodilatation of the arm. In each case the sounds begin with a series of high amplitude swings which interrupt the baseline. The duration of the "snap" in this subject increases as cuff pressure falls and becomes maximal at 40 to 50 mm. Hg below systolic pressure. The rumbling vibrations are best seen at 110 mm. Hg in the normal recording, and in the range 115 to 85 mm. Hg in the exercise recordings. Time is given below as 0.04 second between the vertical white lines.

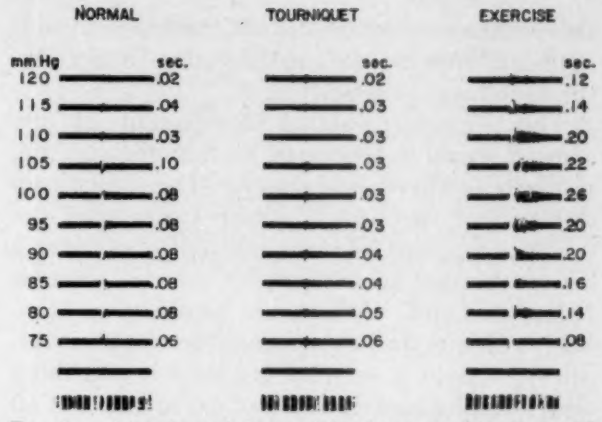

FIG. 2. *Arterial sounds in an eighty-four year old patient with a diagnosis of arteriosclerotic heart disease.* The sounds during a "normal" reading have short durations. Application of a tourniquet reduces the intensity of the sounds. After ischemic exercise the sounds are of much greater intensity and duration.

was at about 30 mm. Hg below the systolic pressure level. The hand exercise also produced another important effect: the muffling phase tended to be eliminated and the sounds continued clearly audible and easily recorded until they disappeared entirely within a beat or two at the previously noted diastolic level. The increased amplitude of the sounds following exercise improved the security of estimation of the diastolic pressure and obviated the need for a choice between the point of muffling or the complete absence of sounds.

CARDIAC PATIENTS

Twenty-five patients with cardiac disease were tested. The arterial sounds in old and seriously ill patients were generally of less intensity and duration than in normal subjects (Fig. 2). These sounds were further diminished in intensity by the application of a tourniquet on the forearm. After exercise of the ischemic forearm the sounds were greatly augmented in amplitude and duration, the loudest sounds being recorded at 25 to 30 mm. Hg below the systolic level. In three patients with obliterative arterial disease, all the sounds were faint and brief, and these were unaffected by the clenching exercise. The six hypertensive patients of the present series had sounds of greatest duration at the same subsystolic levels as normal subjects. Thus, the maximal durations of the sounds appeared to be fixed to the systolic pressure, regardless of its height.

COMMENTS

Components of the Sounds: The "loudness" of the arterial sounds is an impression produced by the combination of the intensity of the snap and duration of the rumble. The untrained ear is usually unable to differentiate these sounds and tends to fuse them together. Arteriophonography assists in the separation of the components and in the evaluation of their respective energies.

At the instant that the rising arterial pulse overcomes the force of compression of the cuff, the artery is blown open and a sharp snapping sound is produced. The amplitude of this snap is dependent on the rate of rise of the pulse wave at the instant of opening of the vessel. This effect can be noted in Figure 1 in which the snap is weak at the systolic and diastolic levels where the slope of the upstroke is normally minimal. Where the slope of the upstroke is steep, as in its midportion, the snap may be very loud, being recorded with a duration of as much as 0.04 second. The amplitude and duration of this component of the sounds are modified somewhat by the freedom of blood flow. Thus, it tends to be somewhat weaker in

the presence of reduced flow (tourniquet) and stronger following the vasodilatation induced by the clenching exercise (Fig. 1).

The second rumbling component of the arterial sound is generated by flow through the partially compressed artery. The maximum duration of the rumble phase varies with the pressure gradient from the segment of the artery above the cuff to that of the arterial segment below the cuff. When the gradient is high, flow is greater and duration of the rumble is relatively long; a reduced gradient is associated with a diminished duration of the sound. In all instances the rumble appeared to be associated with the systolic pressure and relatively independent of the diastolic pressure.

Phases of the Sounds: Four successive phases of arterial sounds, based on quality or loudness, are said to be differentiated during blood pressure measurement.[6] *Phase 1* appears to be due entirely to the snapping sound. The intensity of this sound increases rapidly as the cuff pressure falls below the level of the systolic pressure and as the slope of the upstroke becomes progressively steeper.

Phase 2 of the normal arterial sound begins with the snapping sound, followed by a rumble which increases in duration as the cuff pressure continues to fall to about 20 mm. Hg below systolic pressure in normal subjects and to about 30 mm. Hg after the reactive vasodilatation. An inconstant fading of the sounds in these pressure ranges sometimes occurs in patients with cardiopulmonary disease. However, this effect appears to result from fluctuations in the blood pressure during the ventilatory cycle. The occasional fading of Phase 2 may therefore reflect an abnormal situation.

In *Phase 3* the rumbling sound tends to disappear and only the snapping sound remains. The amplitude of this snap is in relation to the slope of the arterial upstroke at the level of the cuff.

Phase 4 is characterized by a muffling of the sound. This effect may be due in part to the diminished slope at the origin of the upstroke. A second factor may be the tendency for a rise in pressure in the artery beyond the cuff; this distal segment of the artery becomes relatively distended and the tendency to vibration is reduced. Arteriolar dilatation subsequent to exercise of the ischemic arm prevents the rise in distal arterial pressure and consequently converts the muffle into a clearer sound.

The sound disappears entirely when the pressure in the cuff falls below the diastolic pressure in *Phase 5*.

Clinical Significance: The results suggest that attention to the pressure level at which the longest duration of sounds is heard may provide a means for appraising the degree of peripheral vasoconstriction. With the normal arteriolar tone of resting metabolism, the greatest duration occurs at about 20 mm. Hg below the systolic. Reactive vasodilatation results in a marked increase in duration of the arterial sounds, with the maximum occurring about 30 to 35 mm. Hg below systolic pressure.

When blood flow is obstructed, as in arteriolar constriction or organic arterial obstruction, all arterial sounds are of short duration. A reduced duration of the sounds thus calls attention to physiologic or organic factors which limit the blood flow to the periphery.

Summary

Arterial sounds were recorded on forty-five subjects during indirect blood pressure measurements. In normal subjects the sounds increased in duration as cuff pressure fell, becoming maximal at approximately 20 mm. Hg below the systolic level. As the cuff pressure continued to fall, the sounds became shorter and were relatively muffled at the diastolic pressure level. Repeated clenching of the fist induced a local arteriolar vasodilatation in the ischemic extremity, and the arterial sounds were of greater duration, with a maximum at about 30 mm. Hg below the systolic value. The relation between the systolic pressure and the point of maximal duration of the sounds was the same in normotensive and hypertensive patients. Induced reactive hyperemia eliminated the muffling phase of the vibrations and the sounds could be heard clearly until they ended abruptly at the diastolic level. When the blood flow into the extremity was diminished, all the sounds were of short duration.

The phases, mechanisms and clinical utility of the arterial sounds are discussed.

Acknowledgment

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References

1. Korotkoff, N. S. A contribution to the problem of methods for the determination of the blood pres-

sure. In: Classics in Arterial Hypertension. Edited by Ruskin, A. Springfield; Illinois, 1956. Charles C Thomas.

2. Rodbard, S. The significance of the intermediate Korotkoff sounds. *Circulation*, 8: 600, 1953.
3. Rodbard, S., Rubinstein, H. M. and Rosenblum, S. Arrival times and calibrated pulse wave contours determined indirectly by arterial sound recordings. *Am. Heart J.*, 53: 205, 1957.
4. Korns, H. M. The nature and time relations of the compression sounds of Korotkoff in man. *Am. J. Physiol.*, 76: 247, 1926.
5. Rodbard, S. and Ciesielski, J. A relation between the auscultatory gap and the pulse upstroke. *Am. Heart J.*, 58: 221, 1959.
6. Bordley, J., III, Connor, C. A. R., Hamilton, W. F., Kerr, W. J. and Wiggers, C. J. Recommendations for human blood pressure determinations by sphygmomanometers. *Circulation*, 4: 503, 1951.

The Normal Vibrocardiogram

Physiologic Variations and Relation to Cardiodynamic Events*

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ADVANCES IN electronic technics have stimulated exploration into the use of precordial vibrations for cardiac diagnosis. The earliest records were obtained by Marey and Potain[1] in 1885. For the next fifty-five years direct methods of recording apex pulsations were used by American and European investigators.[2–14] The vibrations of the thoracic wall, acting on a sensitive membrane, produced oscillations which were magnified, usually by optical means, and transmitted to a screen or passing film. Dietrich and Dunker,[14] using an esophageal balloon probe, found differences in the time intervals of vibrocardiographic waves in pathologic states. Neither they nor other investigators[15–20] have further evaluated this observation.

With the adaptation of the cathode ray oscilloscope for recording precordial vibrations[15–20] and the development of a linear recording microphone[21] detailed study of precordial vibrations became feasible. Groups of investigators[22,23] began to assess changes in cardiac function through analysis of the subaudible frequencies. Kountz, Gilson and Smith,[15] who coined the term "vibrocardiogram," observed that in abnormal hearts the first vibrational complex was lengthened. Dunn and Rahm,[24] in a study of abnormal hearts, noted that the damaged myocardium could not produce the same vibrational pattern in successive beats.

The modern period of vibrocardiography now has an increasing number of active investigators. In 1956, Groom and Boone[25] introduced the General Motors capacitance microphone (2–500 c.p.s.) which recorded chest vibrations with a high degree of fidelity. Harrison[26–28] and Eddleman et al.[29–35] have been working with the "kinetocardiogram." Much useful data are currently being reported by this group. Mounsey,[36] Rosa,[37] Hollis[39,40] and our group[41] are all currently investigating the precordial vibrocardiogram using modern electronic methods.

METHODS AND TECHNICS

The electronic technics developed in this laboratory for recording vibrations from the precordium have been described in a previous publication.[41]

Patients are studied in a quiet room as free from noise as possible. Ordinary noise and vibrations, however, do not distort the records. The bed used in these studies consists of a four-inch foam latex mattress supported on a canvas cot. This arrangement has been selected on the basis of its tendency to eliminate directly conducted external vibrations.

A warm room and the foam rubber pad afford comfort to the patient and avoid muscle tremor. Records are taken at least one hour after a meal and after fifteen minutes of relaxation. Records are usually taken at the end of expiration, unless it is desired to note the effect of respiration, because at this point in the respiratory cycle the heart is closest to the chest wall and damping is at a minimum.

The transducer, an Altec-Lansing capacitance microphone (model number 165A), is suspended from a horizontal bar over the bed and placed 2 cm. from the left sternal border at the fourth intercostal space. The use of lubricating jelly at the point of pickup maintains good contact with the chest wall and eliminates skin friction. The polarity of the transducer was standardized so that an outward movement of the chest produced an upward deflection of the tracing.

The recording equipment consists of a four channel direct writer and a four channel F.M. tape recorder, permitting a simultaneous recording of vibrocardiogram, phonocardiogram, electrocardiogram and pulse wave.

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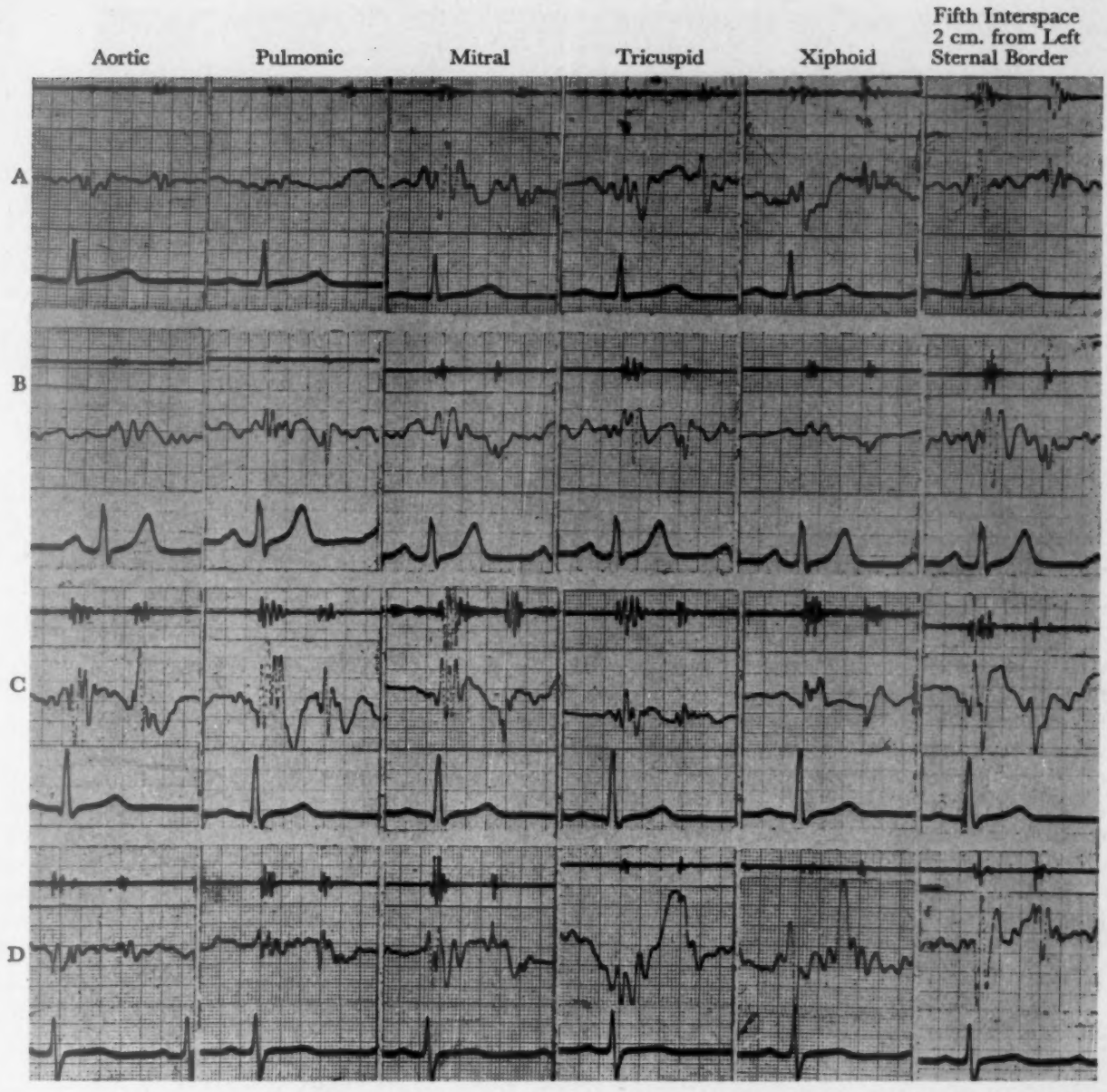

FIG. 1. Vibrocardiographic tracings over six precordial positions in four normal young adults recorded simultaneously with phonocardiogram and electrocardiogram.

The individual vibrocardiographic waves have been designated in accordance with the conventional ballistocardiographic system of lettering.[51]

EXPERIMENTAL STUDIES

HUMAN

Position of Transducer: The character of the vibrocardiogram changes markedly with the variation of the position of the transducer on the chest wall. Figure 1 illustrates the changes at the classic auscultatory areas. These areas may, in the future, have important applications; however, the variations in pattern are too great for present analysis. Therefore, we have selected an area 2 to 3 cm. from the left sternal border in the fourth interspace and have found, as have others,[37–39] that shifts of 1 to 2 cm. do not materially alter the character of the tracings. The records are reproducible from hour to hour (Fig. 2) and, under basal conditions as herein described, from day to day.

Relationship of the Vibrocardiogram to the Electrocardiogram: It was desired to correlate the vibrocardiogram with the electrocardiogram for the purpose of identifying the vibrocardiographic waves. Table 1 shows the data obtained from this study. Only those points which demon-

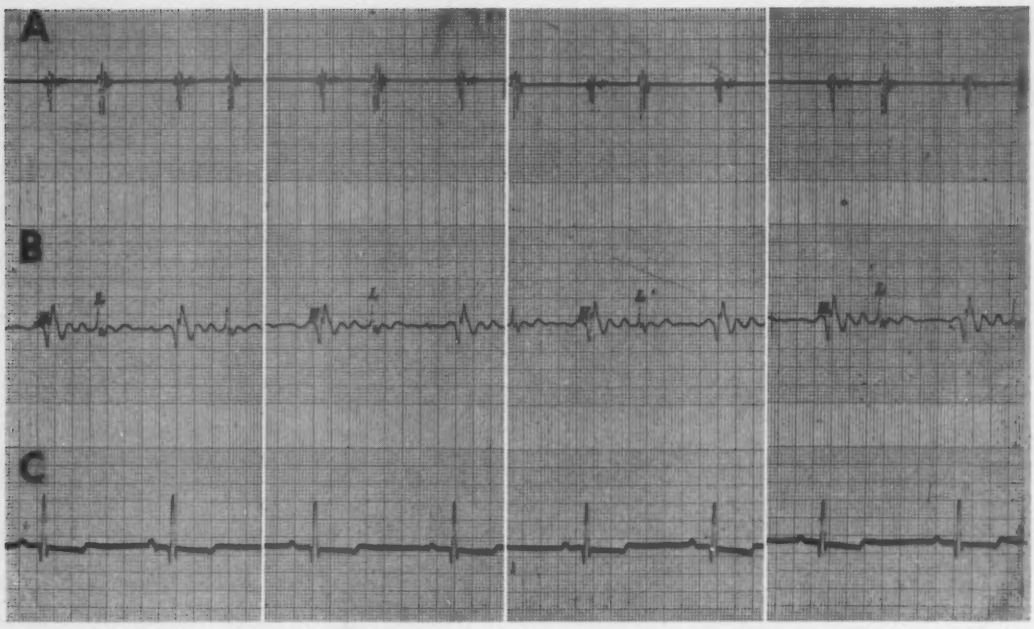

FIG. 2. Consecutive tracings over a period of two hours in normal dog, showing reproducilibity of tracings. A, phonocardiogram. B, vibrocardiogram. C, electrocardiogram.

strated consistent close time relationships are shown. Diastolic waves (those occurring between the N wave of the vibrocardiogram and P wave of the electrocardiogram) had no consistent time relationship. Figure 3 shows the time ranges of each wave with reference to the electrocardiogram. The mean values are indicated in the table.

Effects of Respiration: During the phase of inspiration, damping of the waves is noted (Fig. 4). However, the waves maintain their sharpness and character. During both respiratory phases the H-J_1 interval maintains a constant time relationship to the electrocardiogram while the J_1-J_2 interval is lengthened 0.005 second during the inspiratory phase. With the Mueller test, slight degrees of splitting of the second sound can easily be detected by the vibrocardiogram (Fig. 5). In the first vibrational complex the H-I_1 interval lengthened 0.01 second

TABLE I

Relation of the Vibrocardiogram to the Electrocardiogram before and after Master Two Step Test

Vibrocardiogram Deflection	Electrocardiogram Reference Point	Control (sec.)		After Exercise (sec.)			
				Immediate		15 Minutes after	
		Mean	Range	Mean	Range	Mean	Range
H	R	0.01	0.00–0.02	0.01	0.00–0.02	0.01	0.00–0.02
I_1	S	0.00	0.01–0.02	0.00	0.02–0.02	0.00	0.02–0.02
J_1	S	0.02	0.01–0.04	0.02	0.00–0.04	0.02	0.01–0.04
I_2	S	0.05	0.04–0.06	0.05	0.03–0.07	0.05	0.04–0.07
J_2	S	0.08	0.06–0.10	0.08	0.06–0.10	0.08	0.05–0.10
L_1	T*	0.07	0.06–0.09	0.08	0.06–0.10	0.08	0.06–0.10
M_1	T*	0.09	0.08–0.11	0.09	0.07–0.12	0.09	0.08–0.11
L_2	T*	0.10	0.09–0.10	0.11	0.10–0.12	0.10	0.09–0.10
M_2	T*	0.12	0.12–0.12	0.12	0.08–0.14	0.11	0.10–0.12
N	T*	0.13	0.12–0.14	0.13	0.12–0.13	0.13	0.12–0.14
O	T*	0.16	0.15–0.18	0.16	0.14–0.18	0.16	0.15–0.16
W	T*	0.16	0.15–0.18	0.16	0.14–0.18	0.16	0.15–0.16

* Midpoint.

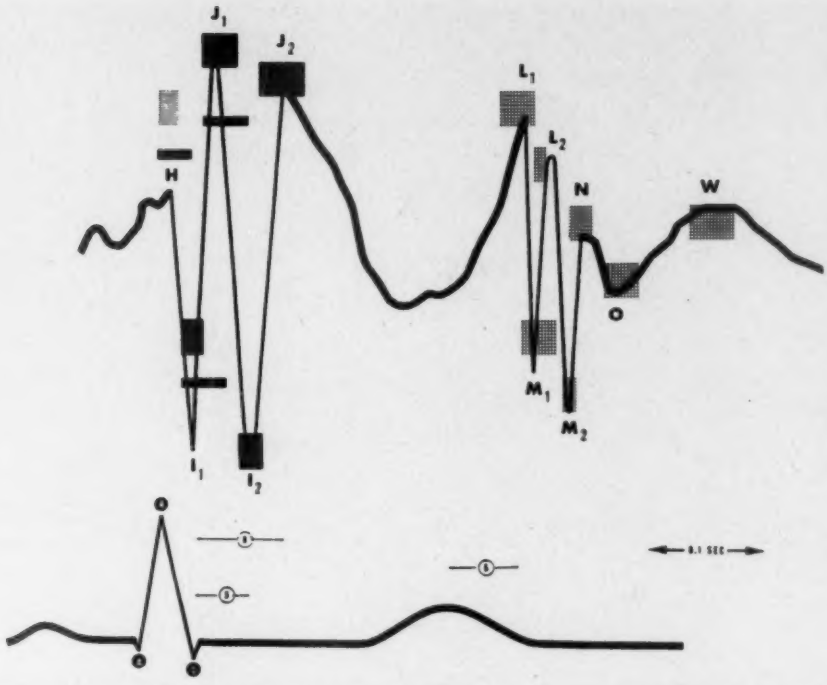

FIG. 3. The timing of the vibrocardiogram with reference to the electrocardiogram. The width of the blocks shows the normal range-variation.

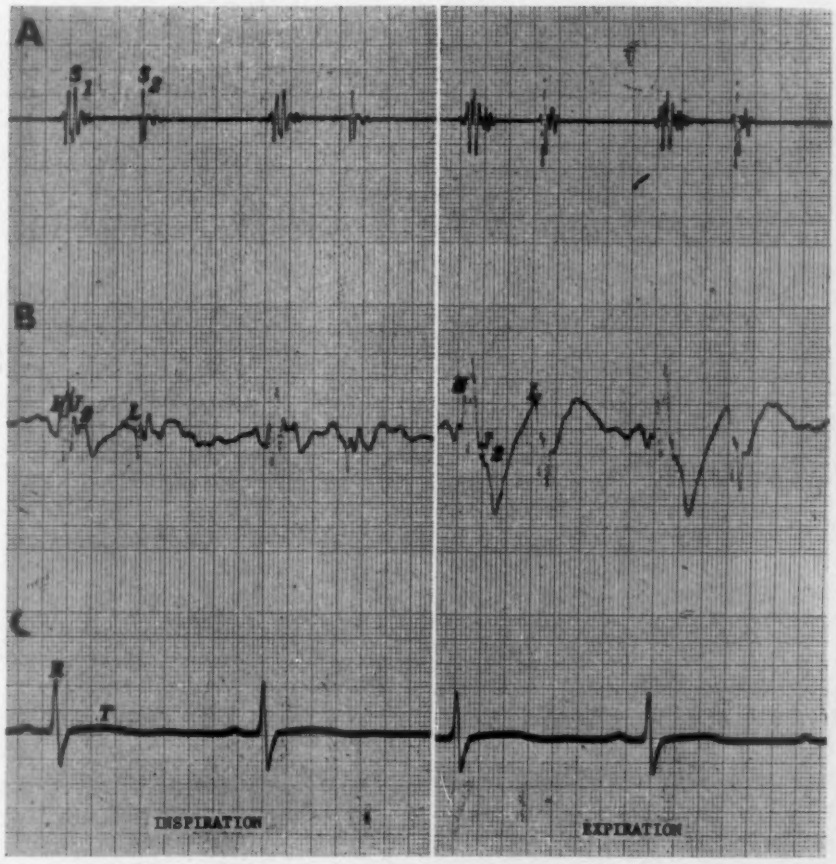

FIG. 4. Respiratory variations. A, phonocardiogram. B, vibrocardiogram. C, electrocardiogram.

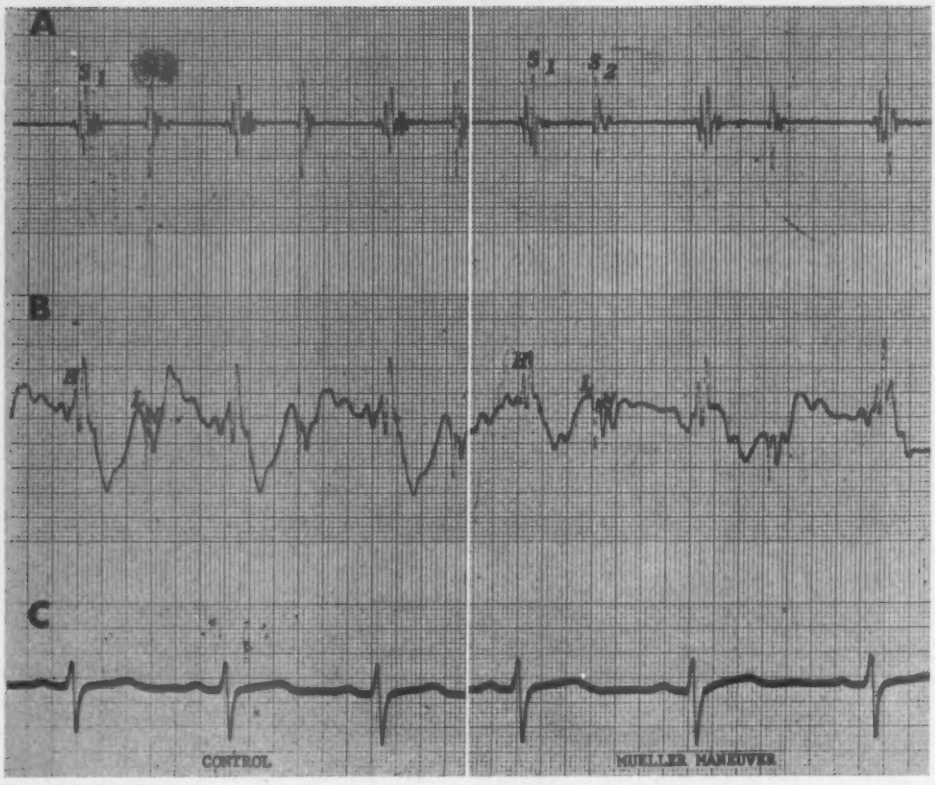

FIG. 5. Respiratory variations. A, phonocardiogram. B, vibrocardiogram. C, electrocardiogram.

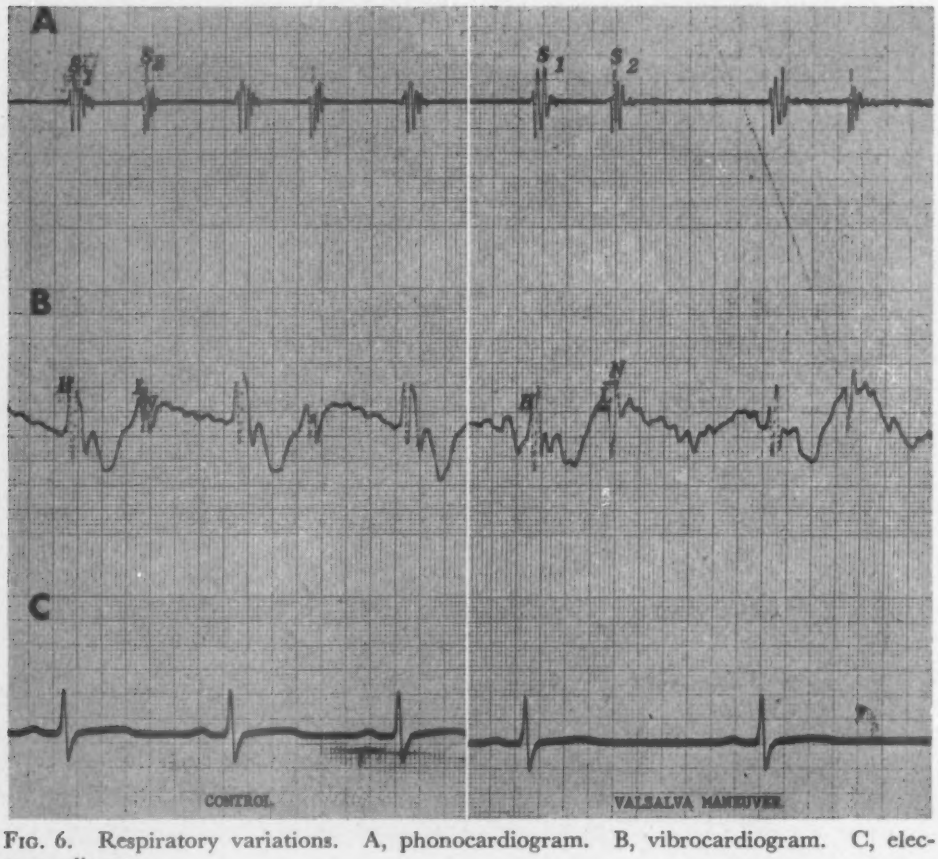

FIG. 6. Respiratory variations. A, phonocardiogram. B, vibrocardiogram. C, electrocardiogram.

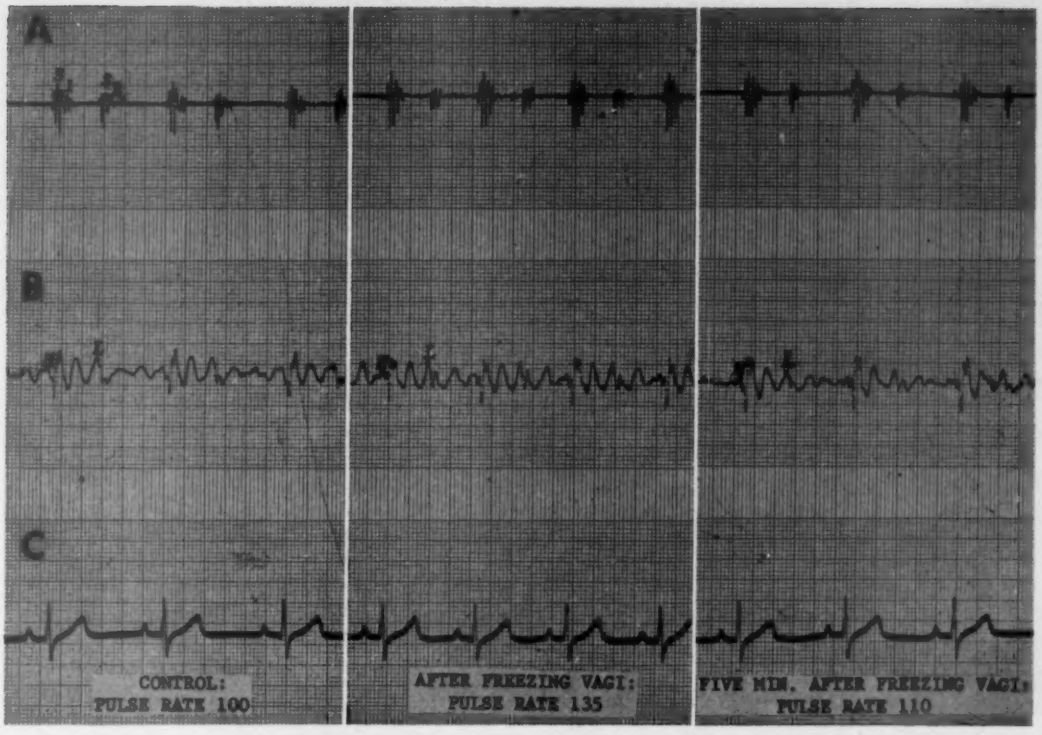

FIG. 7. Influence of pulse rate change on vibrocardiogram. A, phonocardiogram. B, vibrocardiogram. C, electrocardiogram.

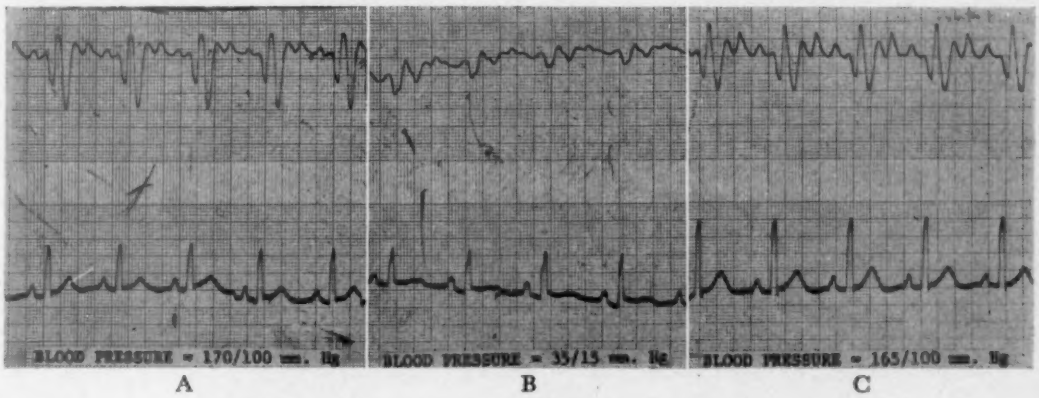

FIG. 8. Influence of blood pressure change.

and the J_1-J_2 interval remained constant; in the second sound complex, L_2-L_3 lengthened 0.03 second.

During the Valsalva test (Fig. 6), a shortening of the H-I and J-J interval by 0.01 second occurred. The L-M complex was not altered.

ANIMAL

Influence of Heart Rate Change: Figure 7 illustrates the pulse rate changes in a typical experiment on a dog before and after freezing the vagi. Although the pulse rates varied, the blood pressure remained unchanged. The only interval of the vibrocardiogram to change was the M_1-L_2, which shortened by approximately 0.005 second. The morphology and amplitude of the waves were not materially altered in any of the experiments.

Effect of Change in Blood Pressure: As illustrated in Figure 8, there is a marked reduction in amplitude of the vibrocardiogram when a fall in blood pressure to a mean level of 35 mm. Hg occurred. The I_1-J_1 interval lengthened 0.01 second. A further reduction in pressure to 25 mm. Hg produced lengthening of J_1-J_2 by 0.02 second and shortening of I_2-J_2 by 0.02 second. An increase in mean pressure to 68 mm. produced further shortening of I_2-J_2 (0.01

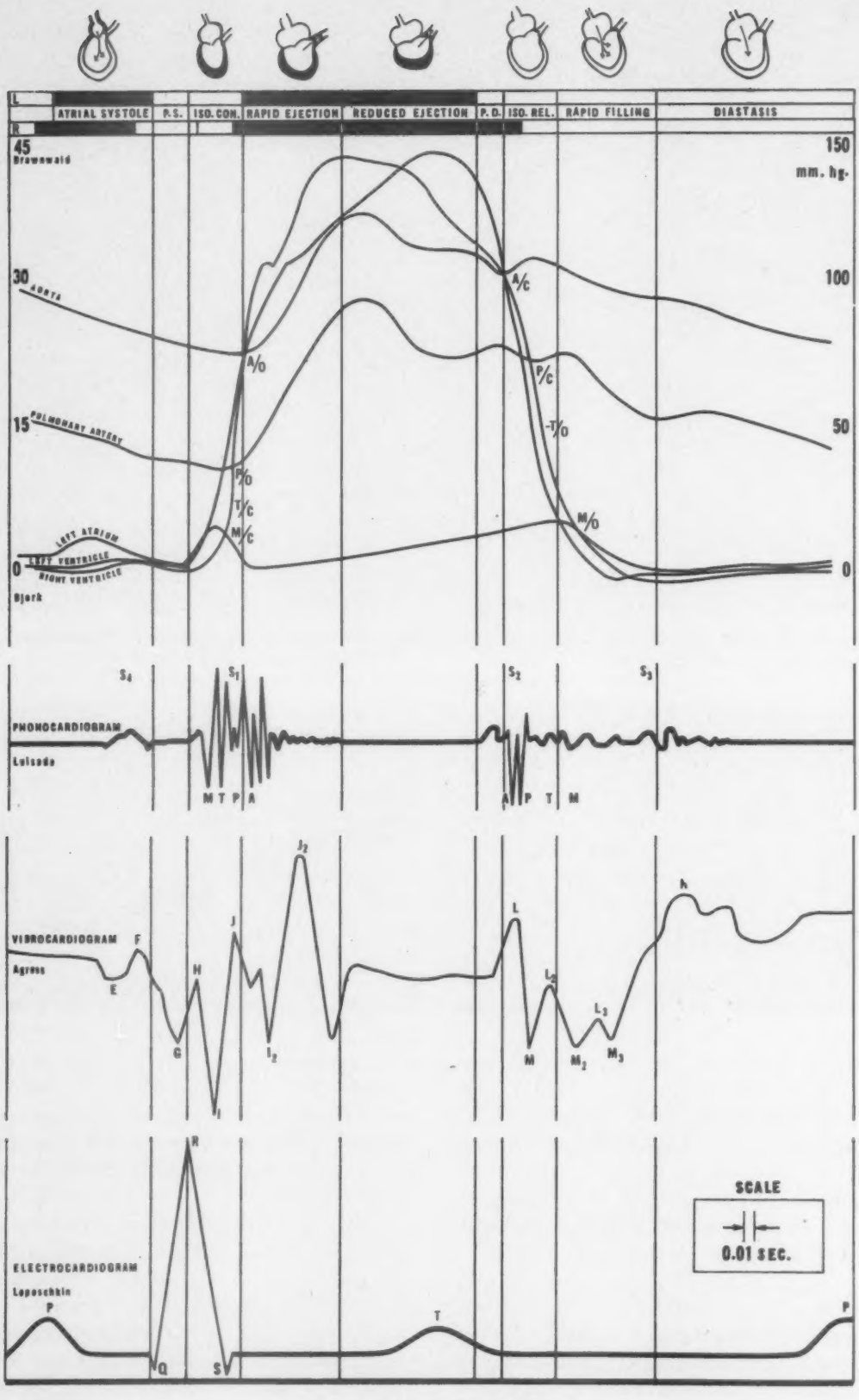

FIG. 9. Events of the cardiac cycle.

second) and a slight increase in amplitude. As pressure increased to 105 mm., the I_1-J_1 interval returned to its control values, as did the amplitude. The entire tracing returned to the preocclusion level when a pressure of 125 mm. Hg was reached.

Relationship of Vibrocardiogram to the Events of Cardiac Cycle: The individual vibrocardiographic waves have been considered to represent the mechanical events of the heart cycle.[36] Figure 9 shows the general relationship of the vibrocardiogram to the events of the cardiac cycle in man. This chart has been constructed from the most appropriate curves obtainable from the literature.[42–47] Although this is a composite graph, an accuracy of 0.005 second per scale division was made possible by using a simultaneously inscribed electrocardiogram as the time base.

A series of experiments on dogs, in which intracardiac pressure, vibrocardiograms and electrocardiograms have been recorded simultaneously, casts doubt upon this relationship in animals. The H wave of the vibrocardiogram occurs simultaneously with the onset of left ventricular isometric contraction; J_2 marks the opening of the semilunar valves, and L_1 marks the closure of the semilunar valve. The period of diastole is characterized by small, low frequency vibrations or a nearly baseline tracing. No consistent pattern in these deflections has yet been found. Thus, in animal studies the vibrocardiographic intervals correlate well with the following periods: isometric contraction (H-J_2), ejection (J_2-L), systole (H-L) and diastole (L-H). These studies, which are now in progress, will be the subject of another report.

Comments

Many studies have been undertaken to correlate ballistocardiographic waves with the events of the heart cycle.[45,48,49] There is still much controversy, however, as to the origin and significance of these ballistic waves. Some of this disagreement arises from the fact that inherent delays between cardiac contraction and graphic inscription of these forces, due in part to equipment and recording technic, are impossible to eliminate.* Hollis[39,40] has recorded vibrocardiograms on twenty subjects during cardiac catheterization. If the timing of the waves is studied substantial agreement will be found with our tracing shown in Figure 9. G follows atrial contraction and H-J_1 corresponds to isometric ventricular contraction. J_1-J_2 occurs simultaneously with rapid ventricular ejection, J_2 peaking near the summit of right ventricular ejection. L occurs simultaneously with the onset of the second heart sound or approximately at the inscription of the dicrotic notch (closure of the semilunar valve). N marks the end of rapid ventricular filling. We have found, as did Rosa,[38] that L_1-L_2 gives better differentiation of the elements of the second heart sound.

Vibrocardiograms (precordial ballistocardiograms) appear to have certain advantages over total body ballistocardiograms. Honig et al.[50] compared ectromelic to normal subjects using a subfrequency pendulum and found that in normal subjects, the ballistocardiogram was distorted "due to inertia, complex mass and loading effects of limb impedance." Both Honig[50] and Hollis[40] found ectromelic subjects free of this impedance, and Hollis[39] found that such records resembled his precordial force-thrust tracings. The problem of damping when the body must be closely coupled to the bed has always been a vexing one when the concern is to record head to foot motions. Since precordial ballistocardiograms represent principally reflections of anterior-posterior motions, the problem of coupling does not appear to have the same significance. An inexpensive, simple and readily available bed is more acceptable than costly and complex systems designed to circumvent damping. Again, vibrocardiographic recording is independent of ordinary floor vibrations and room noises, which makes it a more practical procedure. Due to the inherently high energy level of the vibrocardiogram, normal background vibrations interfere with the record very little as compared to the ballistocardiogram or phonocardiogram. The precordial transducer can easily be attached to the patient in the sitting or semireclining position, which makes it possible to monitor the heart beat during many procedures, including air or space flights.

Summary

The variations in the vibrocardiogram produced by alteration of recording surface and position of the transducer of the precordium are shown. The physiologic effects of respiration, forced breathing, change in heart rate and change in pulse pressure are noted in normal

* Improved equipment in use since this paper was written has eliminated much of the error. (H-J_2) in animal corresponds to isometric contraction.

human subjects and dogs. A study of the characteristics of vibrocardiographic waves indicates that these waves have reproducible characteristics when a standardized technic is used. The timing of the vibrocardiographic waves and their relation to the electrocardiogram and to the events of the cardiac cycle are shown.

Precordial ballistocardiographic tracings (vibrocardiograms) have certain advantages over total body ballistocardiograms. Their relative freedom from limb impedance and damping permits records to be taken upon inexpensive, simple beds. Tracings can be recorded in any position and are not distorted by ordinary floor vibrations or room noises. These records are less distorted by artefacts and, since the time lag is reduced, they closely follow the activity of the heart.

References

1. Marey, E. J. and Potain. La Methode Graphique dans les Sciences Experimentales. Paris, 1885. Masson & Cie.
2. Crehore, A. C. A study of tracings from the region near the apex of the heart. *J. Exper. Med.*, 14: 351, 1911.
3. Crehore, A. C. and Mera, F. S. The micrograph. *J. Exper. Med.*, 13: 616, 1911.
4. Hess, C. Untersuchung der Bewegungen des normalen und pathologischen Herzens sowie der zentralen Gefaesse, mit dem Frank'schen Apparat. *Ergebn. inn. Med. u. Kinderh.*, 14: 370, 1915.
5. Weitz, W. Ueber die Kardiographie am gesunden und pathologischen Herzen. *Ergebn. inn. Med. u. Kinderh.*, 22: 418, 1922.
6. Weitz, W. Ueber die Kardiographie am gesunden Herzen mit dem Frank'schen apparat. Ueber die Kardiographie des pathologischen Herzens mit dem Frank'schen Apparat., *Deutsches Arch. klin. Med.*, 124: 134, 1917.
7. Weber, A. Die Electrokardiographie am gesunden und pathologischen Herzen. *Ergebn. inn. Med. Kinderh.*, 22: 418, 1922.
8. Williams, H. B. and Dodge, H. F. Analysis of heart sounds. *Arch. Int. Med.*, 38: 685, 1926.
9. Pachon, V. and Fabre, R. Le Cardiogramme de Decubitus Lateral Gauche en Clinique. Paris, 1929. G. Doin & Cie.
10. Lewis, J. K. Nature and significance of heart sounds and of apex impulses in bundle branch block. *Arch. Int. Med.*, 53: 741, 1934.
11. Wolferth, C. C. and Margolies, A. Asynchronism in contractions of the ventricles in the so-called common type of bundle branch block: its bearing on the determination of the significant lesion and the mechanism of split first and second heart sounds. *Am. Heart J.*, 10: 425, 1935.
12. Eckstein, R. W. Sounds due to muscular contractions and their importance in auscultatory qualities of the first heart sounds. *Am. J. Physiol.*, 118: 359, 1937.
13. Battro, A., Braun-Menendez, E. and Orias, O. L'asynchronisme ventriculaire dans les blocs de branche. Sa demonstration au moyen de l'enregistrement des phenomenes mecaniques de l'active–cardiaque. *Arch. mal coeur*, 31: 250, 1938.
14. Dietrich, S. and Dunker, E. Untersuchungen uber die Schwingungsvorgange bei der Herzaction. *Arch. Kreislaufforsch.*, 5: 239, 1939.
15. Kountz, W. B., Gilson, A. S. and Smith, J. R. The use of the cathode ray for recording heart sound and vibrations. I. Studies on the normal heart. *Am. Heart J.*, 20: 667, 1940.
16. Smith, J. R., Gilson, A. S. and Kountz, W. B. The use of the cathode ray for recording heart sounds and vibrations. II. Studies on the muscular element of the first heart sound. *Am. Heart J.*, 21: 17, 1941.
17. Smith, J. R., Edwards, J. C. and Kountz, W. B. The use of the cathode ray for recording heart sounds and vibrations. III. Total cardiac vibrations in 100 normal subjects. *Am. Heart J.*, 21: 228, 1941.
18. Kountz, W. B. and Smith, J. R. Total cardiac vibrations in aged hearts and in coronary disease. *Proc. Soc. Exper. Biol. & Med.*, 47: 353, 1941.
19. Kountz, W. B. and Smith, J. R. Studies on the early recognition of myocardial disease by use of the vibrocardiogram. *South. Med. J.*, 35: 713, 1942.
20. Kountz, W. B., Wright, S. T. and Sturm, R. E. Comparisons of total vibrations obtained in myocardial disease. *Am. Heart J.*, 27: 396, 1944.
21. Rappaport, M. B. and Sprague, H. B. The graphic registration of the normal heart sounds. *Am. Heart J.*, 23: 591, 1942.
22. Luisada, A. A. and Magri, G. The low frequency tracings of the precordium and epigastrium in normal subjects and cardiac patients. *Am. Heart J.*, 44: 545, 1952.
23. Down, M. Vibrocardiography—a study of vibrations in the normal heart. *Australasian Ann. Med.*, 5: 54, 1956.
24. Dunn, F. L. and Rahm, W. E., Jr. The visual study of heart vibrations and sounds as transmitted through the precordium. *J. Ins. Med.*, 1: 4, 1949.
25. Groom, D. and Boone, J. A. The recording of heart sounds and vibrations. II. The application of an electronic pickup in the graphic recording of subaudible and audible frequencies. *Exper. Med. & Surg.*, 14: 255, 1956.
26. Harrison, T. R., Lowder, J. A., Hefner, L. L. and Harrison, D. C. Movements and forces of the human heart. V. Precordial movements in relation to atrial contraction. *Circulation*, 18: 82, 1958.
27. Harrison, T. R., and Norman, J. R. Movements and forces of the human heart. IV. Precordial movements (kinetocardiograms) in relation to ejection and filling of the ventricles. *Arch. Int. Med.*, 101: 582, 1958.
28. Harrison, T. R. Movements of the heart and velocity of pressure change during the first part of systole. *Bull. Johns Hopkins Hosp.*, 104: 290, 1959.
29. Eddleman, E. E., Willis, K., Reeves, T. J., and Harrison, T. R. The kinetocardiogram. I. Method of recording precordial movements. *Circulation*, 8: 269, 1953.
30. Eddleman, E. E., Willis, K., Christianson, L.,

PIERCE, J. R. and WALKER, R. P. The kinetocardiogram. II. The normal configuration and amplitude. *Circulation*, 8: 370, 1953.

31. EDDLEMAN, E. E. and WILLIS, K. The kinetocardiogram. III. Distribution of forces over the anterior chest. *Circulation*, 8: 569, 1953.
32. EDDLEMAN, E. E., HEFNER, L. REEVES, J. J. and HARRISON, T. R. Movements and forces of the human heart. *Arch. Int. Med.*, 99: 401, 1957.
33. EDDLEMAN, E. E. Kinetocardiographic findings in aortic insufficiency. *Am. Heart J.*, 53: 530, 1957.
34. EDDLEMAN, E. E., TUCKER, W. L. and KNOWLES, J. L. Mitral insufficiency; cardiac mechanics as studied with the kinetocardiogram and ballistocardiogram. *Circulation*, 12: 278, 1955.
35. EDDLEMAN, E. E. and SUH, S. K. Kinetocardiographic findings of myocardial infarction. *Circulation*, 19: 531, 1959.
36. MOUNSEY, P. Precordial ballistocardiography. *Brit. Heart J.*, 19: 259, 1957.
37. ROSA, L. M. Einfuhrung in die Ballistische Kardiographie. Munster, 1958. Verlag Regensberg.
38. ROSA, L. M. The displacment vibrocardiogram of the precordium in the low frequency range. *Am. J. Cardiol.*, 4: 191, 1959.
39. HOLLIS, W. J. Preliminary observations on the relation of the precordial force-thrust to intracardiac pressure. *Exper. Med. Surg.*, 16: 127, 1958.
40. HOLLIS, W. J. Time relations of the precordial force-thrust and the acceleration ballistocardiogram from a pendulum and ball bearing platform. *Exper. Med. Surg.*, 16: 116, 1958.
41. AGRESS, C. M. and FIELDS, L. G. A new method for analyzing heart vibrations. I. Low frequency vibrations. *Am. J. Cardiol.*, 4: 184, 1959.
42. BJORK, V. O. Left ventricular pressure measurement in man. *Am. Heart J.*, 48: 8, 1954.
43. LEPSCEHKIN, E. Modern Electrocardiography, p. 222. Baltimore, 1951. Williams & Wilkins Co.
44. LUISADA, A. A., LIU, C. K., ARAVONIS, C., TESTELLI, M. and MONIS, J. On the mechanism of the production of the heart sounds. *Am. Heart J.*, 55: 383, 1958.
45. SCARBOROUGH, W. R. The nature of records from ultra-low frequency BCG systems and their relations to circulatory events. *Am. J. Cardiol.*, 5: 613, 1958.
46. BRAUNWALD, E., MOSCOVITZ, H. L., AMRAM, S. S., LASSER, R. P., SAPIN, S. O., HIMMELSTEIN, A., RAVITCH, M. and GORDON, A. J. Timing of the electrical and mechanical events of the left side of the human heart. *J. Appl. Physiol.*, 8: 309, 1955–56.
47. COBLENTZ, B., HARVEY, R. M., FERRER, M. I., COURNAND, A. and RICHARDS, D. W. The relationship between electrical and mechanical events in the cardiac cycle of man. *Brit. Heart J.*, 11: 1, 1949.
48. TANNENBAUM, O., SCHACK, J. A. and VESELL, H. Relationship between ballistocardiographic forces and certain events in the cardiac cycle. *Circulation*, 6: 586, 1952.
49. REEVES, T. J., HEFNER, L. L., JONES, W. B. and SPARKS, J. E. Wide frequency range force ballistocardiogram, its correlation with cardiovascular dynamics. *Circulation*, 16: 43, 1957.
50. HONIG, C. R. and TENNY, S. M. Influence of the limbs on the ballistocardiogram. *Am. Heart J.*, 54: 678, 1957.
51. SCARBOROUGH, W. R. and TALBOT, S. A. Proposals for ballistocardiographic nomenclature and conventions: revised and extended. *Circulation*, 14: 435, 1956.

Experimental Studies

Effect of the Cardiac Arrhythmias on the Renal and Mesenteric Circulations*

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THE PURPOSE OF the present study was to determine the effect of cardiac arrhythmias on the renal and mesenteric circulations and to study the role played by the organs of these systems in circulatory homeostasis during cardiac arrhythmias. The blood flow in a renal artery and in a branch of the superior mesenteric artery was measured with a new electromagnetic flowmeter with an electronic integrator-computer.[1] This instrument accurately measures the volume of blood flow directly and instantaneously over a predetermined period of time and eliminates the need for cannulation of the artery or for the introduction of anything that induces turbulence or causes obstruction to the flow of blood.

This technic for measurements of renal flow is more accurate than renal clearance studies which are indirect and depend upon the functional integrity of tubular and glomerular cells. Selkurt[2] has demonstrated that indirect clearance studies in the presence of renal ischemia or hypotension are not reliable. Because arrhythmias frequently induce hypotension, renal ischemia undoubtedly occurs; hence, indirect measurements of renal blood flow may be erroneous.

TECHNIC

Thirty-two mongrel dogs weighing from 13.5 to 22.5 kg. were anesthetized with sodium pentobarbital intravenously (2.3 cc. per kg.). An intratracheal cannula was inserted and connected to a pump respirator for positive pressure breathing. The left side of the chest was opened between the fourth and fifth ribs, the lung retracted and the pericardium exposed and incised to allow easy access for stimulation of the left atrium and ventricle. A catheter connected to a Statham strain gauge was inserted into the right femoral artery for measurement of the systemic blood pressure. The right femoral vein was cannulated for the administration of intravenous fluids as required. The strain gauge and lead II of the electrocardiogram were connected to a multichannel photographic recorder (Electronics for Medicine). In eighteen animals the abdomen was opened by a right paramedian incision and a retroperitoneal exposure of the right kidney and renal artery made. An electromagnetic probe with a lumen diameter of 3 mm. was placed around the renal artery. Zero flow was established by momentary occlusion of the renal artery with a rubber-shod hemostat and the flowmeter was set at zero. The abdomen was then closed, allowing only the electrode leads to emerge through the incision. In fourteen animals a median abdominal incision was made and a branch of the superior mesenteric artery supplying a portion of the ileum was isolated. An electromagnetic probe with a lumen diameter of 1 mm. was applied to the vessel. The branch of the mesenteric artery around which the electromagnetic probe was placed was momentarily occluded approximately 1 inch distal to the electromagnetic probe so the flowmeter could be set at zero. The abdomen was then closed with the leads of the probe emerging from the incision.

Electrical contact of the vessel wall with the electrodes and the ground cuffs which are within the lumen of the probe was enhanced by surrounding the area with saline or blood during the course of the experiment. The magnet and electrode leads were attached to an Avionics† electromagnetic flowmeter

† Avionics Research Products Corp., Venice, California.

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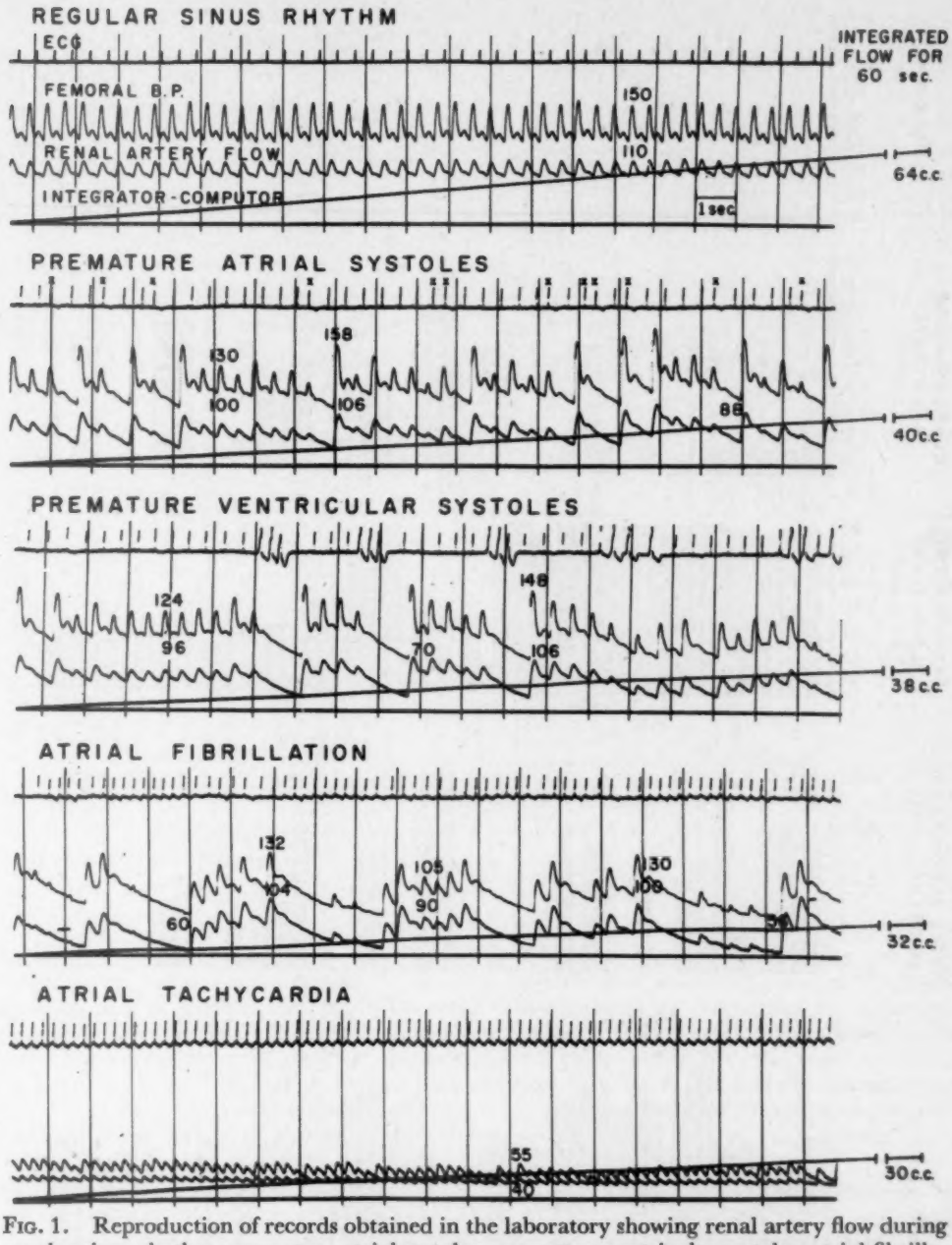

FIG. 1. Reproduction of records obtained in the laboratory showing renal artery flow during regular sinus rhythm, premature atrial systoles, premature ventricular systoles, atrial fibrillation and atrial tachycardia. Note the progressive reduction in the renal artery flow during these arrhythmias.

and computer system, and then to the multichannel recording machine. Because it is extremely difficult during cardiac arrhythmias to measure the area under the flow trace to determine the volume flow, we used an integrator-computer which accurately and instantaneously totals this flow for any predetermined period of time. An automatic timing device, preset for a thirty second period, automatically integrated the blood flow for that interval and then returned to zero. After the probe had been applied control tracings were obtained over a period of several hours to insure that the flow was consistent and that the probe did not induce spasm of the renal or mesenteric artery. The technic is described elsewhere.[1]

Cardiac Arrhythmias: When control readings had been established and recorded, premature atrial systoles were induced by stroking the exposed atria with a wooden applicator for two or more thirty second periods. Following this, further control tracings were obtained and then premature ventricular systoles were created by stroking the left ventricle. Tincture of aconitine was then applied to the left atrial appendage and this produced either paroxysmal atrial tachycardia or fibrillation or both. Ventricular tachycardia was later produced by

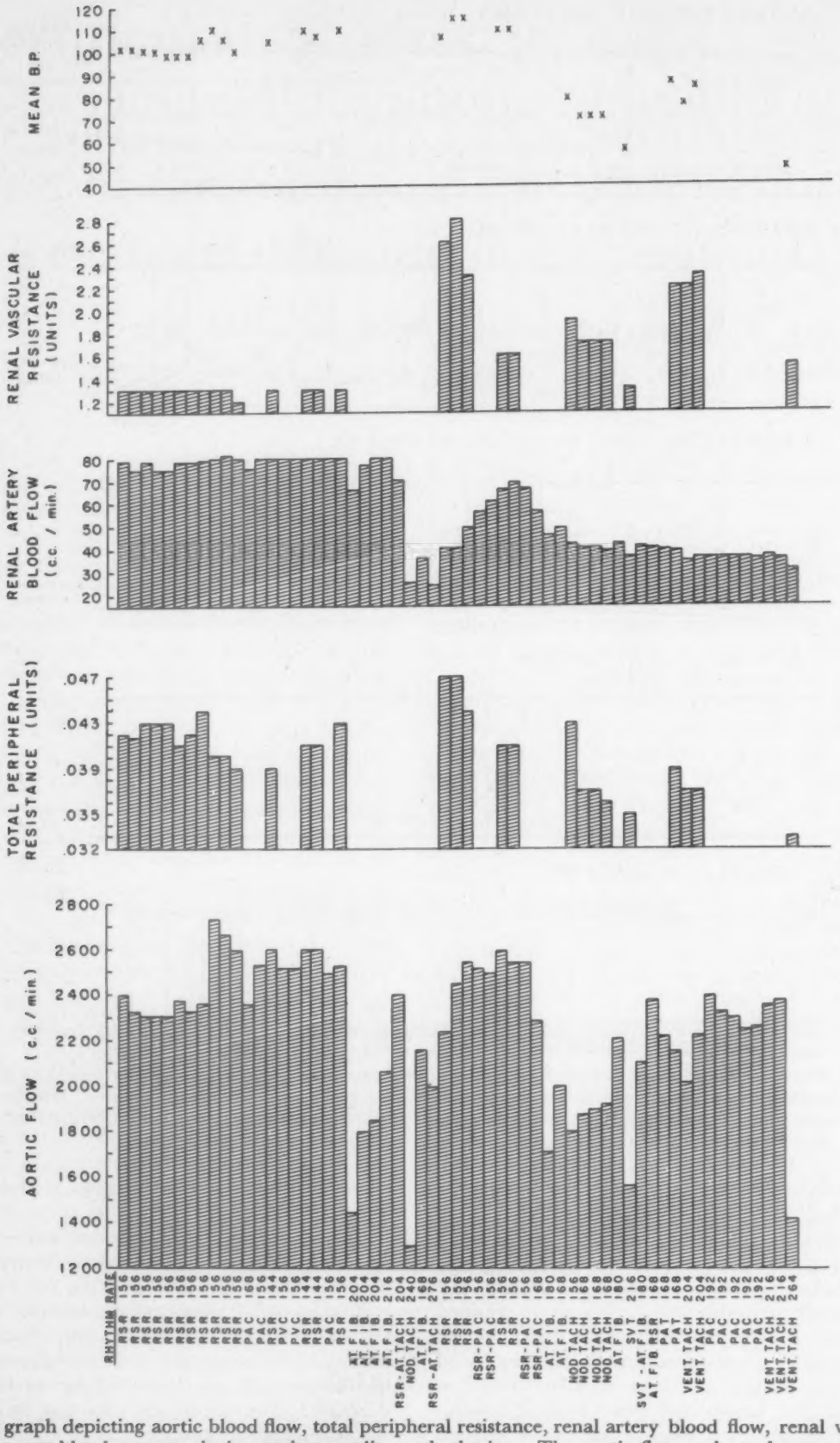

FIG. 2. Bar graph depicting aortic blood flow, total peripheral resistance, renal artery blood flow, renal vascular resistance and mean blood pressure during various cardiac arrhythmias. The aortic flow and renal artery blood flow were measured simultaneously. Note the discrepancy between the changes in the aortic flow and the renal artery blood flow as well as in the total peripheral resistance and the renal vascular resistance. Abbreviations as in Figure 3.

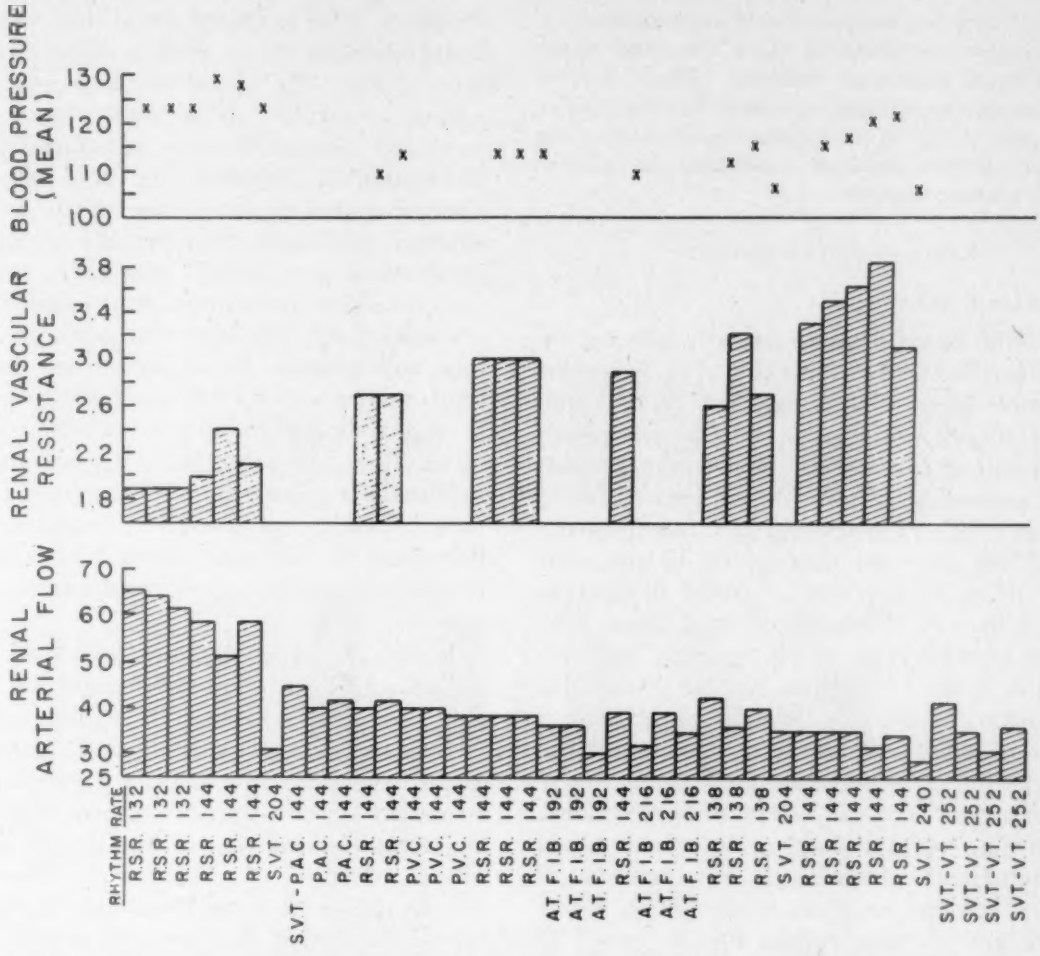

FIG. 3. Bar graph showing renal artery blood flow, renal vascular resistance and mean blood pressure during various arrhythmias. Note the progressive decrease in the renal artery flow corresponding to a progressive increase in the renal vascular resistance throughout the course of the experiment. Near the end of the experiment when regular sinus rhythm was restored, the renal flow remained at values approximately two-thirds of control values, while the resistance had increased from 1.8 to 3.8 units. R.S.R. = regular sinus rhythm; S.V.T. = supraventricular tachycardia; P.A.C. = premature atrial contractions; P.V.C. = premature ventricular contractions; At. Fib. = atrial fibrillation; and V.T. = ventricular tachycardia.

applying the tincture of aconitine to the ventricle. Ethyl chloride spray was used to cool the aconitine focus and thus convert the arrhythmia to normal sinus rhythm. After each episode of atrial and ventricular premature systoles, tachycardia and atrial fibrillation, control flows were recorded during lengthy periods of normal sinus rhythm. The electrocardiogram, femoral arterial blood pressure, blood flow trace, integrator-computer trace and a base line marker were recorded simultaneously (Fig. 1).

In two experiments, the aortic flow was measured with a second electromagnetic flowmeter simultaneously with the renal artery blood flow (Fig. 3).

Calibration: Probes were calibrated at the end of each experiment.[1] This eliminated day to day variations which included inadvertent changes in control or gain settings on either the flowmeter or the recording machine, positioning technic, or changes in the specific gravity, hematocrit, etc., of the dog's blood. Because of the short length of the renal artery of the dog, artificial calibration with the use of a specially designed apparatus was done at the end of each experiment. This calibration apparatus consists of an aluminum jacket into which the probe is snugly inserted and known quantities of blood were collected at various flow rates in a graduated cylinder and integrated over a thirty second interval. These results were then averaged so that the integrator slope for a thirty second period represented a known volume of flow. From this calibration technic, it was determined that the over-all accuracy of this instrument is plus or minus 5 per cent. Although the flow through only one renal artery was measured, we believe that this reflects the changes in the total renal circulation.

When the mesenteric blood flow was measured, the probe was calibrated *in situ* on the vessel. The

mesenteric artery was cannulated approximately 2 inches distal to the probe to allow the blood to be diverted to a graduated cylinder. Three or five calibration determinations were made by collecting at various rates of flow in the graduate while integrating for a thirty second period to insure that the calibration had a linear response.

Results and Comments

RENAL BLOOD FLOW

The renal blood flow is markedly affected by various cardiac arrhythmias (Fig. 1). Frequent premature atrial systoles caused an average drop of 10 per cent (range 4 to 15 per cent), while frequent premature ventricular systoles caused an average drop of 8 per cent (range 2 to 12 per cent). Paroxysmal atrial tachycardia reduced the flow an average of 18 per cent (range 10 to 40 per cent). Atrial fibrillation caused a greater reduction of renal blood flow with an average drop of 20 per cent (range 9 to 60 per cent). The flow during ventricular tachycardia decreased as much as 60 per cent.

Renal Vascular Resistance: When normal sinus rhythm was re-established immediately following short paroxysms of premature systoles, tachycardia, or fibrillation, the renal blood flow remained diminished for periods of time up to one or two hours. The blood pressure and cardiac output had returned to normal; therefore, it is most probable that the reduced blood flow was due to increased renal vascular resistance. The degree of vascular resistance increased during the course of repeated arrhythmias. The renal vascular resistance could only be calculated when the systemic blood pressure was stable during the period of observation. Therefore, it is impossible to calculate resistance factors during irregular rhythms. Therefore, in an experiment with repeated arrhythmias, it must be recognized that it is difficult to calculate an exact percentage reduction in blood flow in a specific arrhythmia because of this progressive degree of renal vasoconstriction. It is also difficult to choose control figures to calculate an average reduction in blood flow. However, we attempted to compare figures obtained early in the experiment when other factors were stable and control flows were reproducible (Fig. 2). Figure 3 also shows the marked progressive increase in renal vascular resistance following repeated arrhythmias (calculated in units as mean systemic blood pressure divided by renal artery blood flow in cubic centimeters per minute). This persisted for at least one or two hours following the conversion of the arrhythmia even though the blood pressure and cardiac output returned to normal limits. This increased resistance was accompanied by a corresponding reduction in renal blood flow. Further studies must be designed to demonstrate whether the vasospastic element is due to the presence of a humoral substance, such as a catecholamine, or to neurogenic control.

Figure 3 demonstrates that when an arrhythmia was present for a significant length of time or when various arrhythmias were produced in rapid succession, a marked drop in renal blood flow was observed. In all cases, this persisted for a variable but prolonged period of time. The renal vascular resistance factor increased (in this case) from 1.9 to 3.8 units, representing severe renal vasospasm and ischemia.

Factors Producing Reduced Renal Flow: Many factors affect the renal flow during an arrhythmia, the most important being the *reduction in cardiac output and systemic blood pressure.* An atrial tachycardia with a relatively well sustained systolic pressure allows much higher renal blood flows than a tachycardia with the blood pressure at hypotensive levels. The *cardiac rate* is also an important determinant. Atrial fibrillation with a rapid ventricular rate (above 200 per minute) will cause a more marked drop in blood flow than atrial fibrillation with a slower ventricular rate.[3] This, however, may be a reflection of the reduced cardiac output and the lower level of blood pressure because hypotension is more liable to occur with a more rapid cardiac rate.

Another factor which appears to affect renal blood flow is the *status of the myocardium.* In the course of these experiments it was noted that if there was myocardial injury or cardiac dilatation due to heart failure, renal flow usually decreased. This also is undoubtedly a reflection of a reduced cardiac output due to the myocardial failure.

We did not attempt to determine the actual site of vasoconstriction in the renal circulation or whether the mechanism was humoral or neurogenic.[4,5] The calculation of resistance factors only indicates an increased resistance in either the renal artery or in the parenchyma of the kidney itself.

Aortic Flow and Peripheral Resistance: When the renal and aortic blood flows were recorded simultaneously (Fig. 2) the aortic flow and the

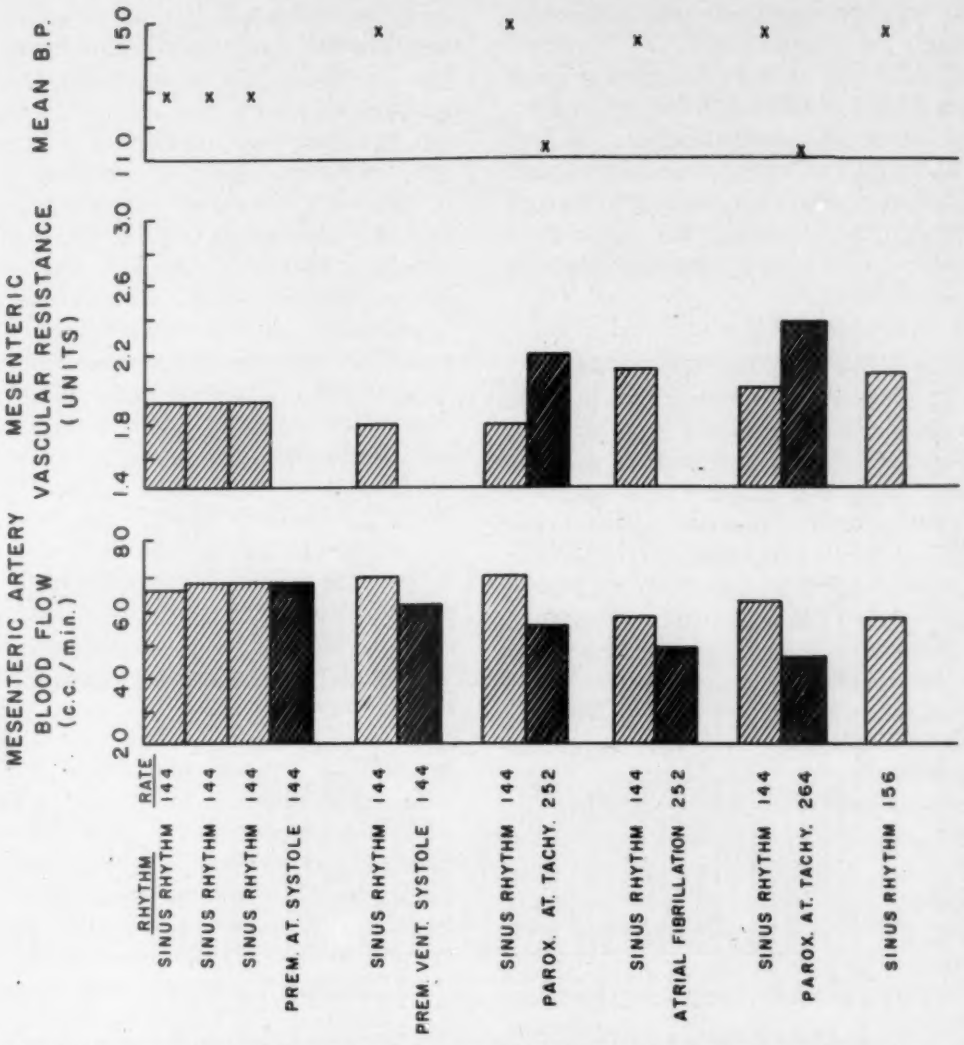

FIG. 4. Bar graph depicting mesenteric artery blood flow, mesenteric vascular resistance and mean blood pressure during various arrhythmias. Note the increase of the mesenteric vascular resistance during paroxysmal atrial tachycardia. Corresponding to this, the mesenteric artery blood flow decreased but tended to return to nearly normal values upon conversion to normal sinus rhythm. Premature atrial and ventricular systoles reduced the blood flow but little.

total peripheral resistance fluctuated and often did not parallel the circulatory changes in the kidney. When the total peripheral resistance increased following arrhythmias it returned to normal almost immediately upon conversion of the arrhythmia, but that of the kidney frequently remained elevated This suggests that the kidney plays a predominant role but is not the sole organ in the maintenance of homeostasis during arrhythmias. The circulation of other organs and tissues must also play a role.

Role of Kidney in Homeostasis during Arrhythmias: Because 25 per cent of the cardiac output serves to supply the kidney, this organ plays a vital role in the homeostatic mechanism by virtue of vasoconstriction.[6,8–10] A decrease in the renal blood flow during the arrhythmias thus allows a relatively large quantity of blood to be made available to the general circulation. This increased amount of "available" blood is utilized by the brain and myocardium, the vital organs least able to withstand any degree of ischemia.[1,7,8,9,11] However, this homeostatic mechanism may cause ischemia and necrosis of the kidney. This condition has been observed clinically following ventricular tachycardia.[12] These experimental studies suggest that various degrees of renal ischemia occur during and immediately following many arrhythmias. The renal damage caused by this ischemia is probably of a significant degree only when an arrhythmia is of long duration.

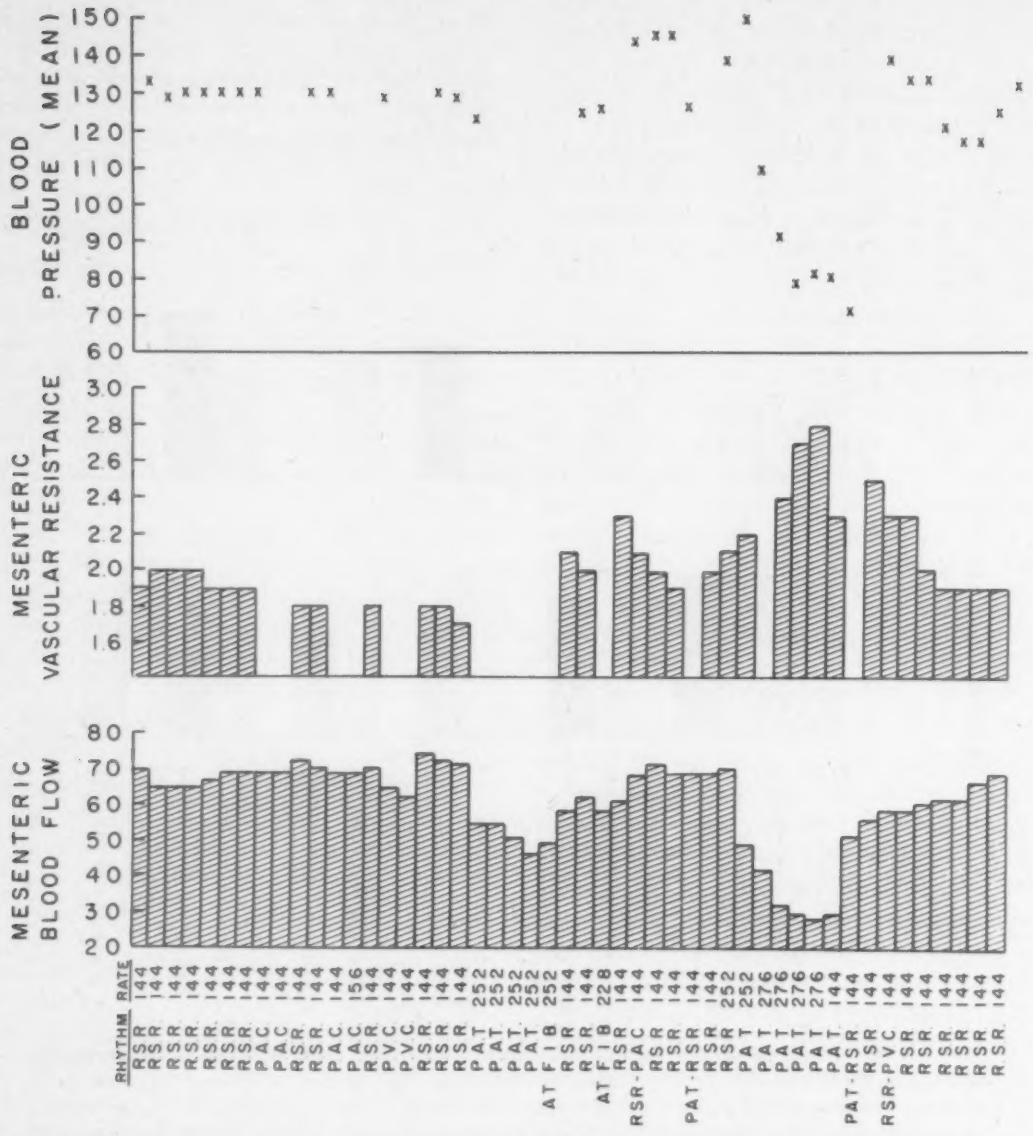

FIG. 5. Bar graph depicting mesenteric artery blood flow, mesenteric vascular resistance and mean blood pressure during various cardiac arrhythmias. Note the reduction in blood flow during the arrhythmias, with a tendency for the flow to return to normal values on conversion to normal sinus rhythm. Abbreviations as in Figure 3.

MESENTERIC BLOOD FLOW

We have noted when measuring the mesenteric circulation that the results were variable due to physiologic changes in the mesenteric vascular resistance. Atrial and ventricular premature systoles decreased the mesenteric artery blood flow very little and sometimes not at all. However, paroxysmal atrial tachycardia reduced the flow an average of 28 per cent (range 10 to 40 per cent) and atrial fibrillation reduced it an average of 34 per cent (range 9 to 50 per cent). Upon conversion to normal sinus rhythm after atrial tachycardia or fibrillation, the flow usually returned to nearly normal control levels promptly. This rapid return of the flow to normal values is unlike the response that we have previously described in the cerebral[1] or renal circulations. However, when we calculated the resistance factor it was noted that it increased during a tachycardia and momentarily remained increased following conversion to regular sinus rhythm (Figs. 4 and 5).

Difference in Response of Mesenteric, Renal and Cerebral Circulation: In spite of the marked increase in the mesenteric vascular resistance which occurred during cardiac arrhythmias, it invariably returned to near normal values soon

after conversion to normal sinus rhythm (Fig. 5). This, again, is different from the response that we have observed in the cerebral[1] and renal circulations. In the renal circulation, the resistance progressively increased as the experiment progressed. Conversely, in the cerebral circulation, the resistance increased to a maximum early in the experiment, almost immediately following the production of one of the first arrhythmias, and remained at this elevated level for the balance of the experiment.[1] In contrast, the mesenteric vascular resistance was more labile and constantly fluctuating. This labile mechanism is probably important for the correction of circulatory homeostasis due to the arrhythmias. Because of the constantly changing resistance, a large quantity of blood within the mesenteric circulation (15 to 18 per cent of the cardiac output)[6] can be shunted to more susceptible and vital areas such as the brain or the heart during an arrhythmia.

Pathologic Changes Secondary to Mesenteric Vascular Insufficiency: We have observed that many patients in arrhythmic shock present with symptoms of abdominal distress, including nausea and vomiting, abdominal pains, distension, anorexia and sometimes diarrhea with or without blood. Patients who have come to autopsy following arrhythmias have sometimes demonstrated ischemic changes which have been called hemorrhagic duodenitis[13] or hemorrhagic necrosis of the gastrointestinal tract.[14] These pathologic changes are probably an expression of ischemia of the bowel which has resulted from a marked decrease in blood supply secondary to the increased mesenteric vascular resistance.[9,23] The syndrome of "mesenteric vascular insufficiency" would, therefore, be an appropriate functional term.

Necrosis of the gut due to a previously unexplained cause has been reported in congestive heart failure, hemorrhagic and postoperative shock, pheochromocytoma, as well as following myocardial infarction.[15–22]

Humoral and Neurogenic Factors in Hemodynamic Changes: In previous experiments,[9,23] it was noted that when vasopressor agents were used to raise the systemic blood pressure the mesenteric vascular resistance increased markedly and the mesenteric blood flow diminished further. At times, the mesenteric circulation appeared to shut down almost completely. This response allows a large volume of blood to be diverted to more vital centers. Others have demonstrated changes in mesenteric vascular resistance due to catecholamines.[24–26] The changes in the mesenteric resistance during cardiac arrhythmias might be induced by the liberation of humoral substances such as catecholamines. However, appropriate experiments have yet to be devised to determine if these hemodynamic changes in the mesenteric circulation are mediated by these humoral substances or by a neurogenic mechanism.

Summary

A new accurate method of direct measurement of renal and mesenteric blood flow is described using a new electromagnetic flowmeter technic with an integrator-computer apparatus.

Using this technic, the effect on the renal circulation of various experimentally produced cardiac arrhythmias was studied. There was a significant reduction in renal arterial flow and a consistent and prolonged rise in the renal vascular resistance. This reduction in renal blood flow due to the increased resistance appears to be a homeostatic mechanism which helps to provide "available" blood for the myocardial and cerebral circulations during arrhythmias. The decrease in renal blood flow often persisted even after conversion to sinus rhythm and a return to normal of the systemic blood pressure and cardiac output. This phenomenon is most likely due to prolonged renal vasoconstriction. Arrhythmias of long duration may result in renal damage due to ischemia.

The results in the mesenteric circulation were more variable. It has been shown that the mesenteric circulation is extremely important in maintaining circulatory homeostasis during arrhythmic shock and is a labile mechanism. For this reason, the mesenteric circulation could be called the "homeostatic watchdog" of the systemic circulation. The term "mesenteric vascular insufficiency" describes the functional state of reduced mesenteric flow due to mesenteric vasospasm and reduced cardiac output and blood pressure which occurs in arrhythmias and other circulatory disturbances. A correlation has been made between these experimental findings and with clinical states seen in patients at the bedside and the autopsy table who present with symptoms of "mesenteric vascular insufficiency."

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References

1. Corday, E. and Irving, D. W. The effect of the cardiac arrhythmias on the cerebral circulation. *Am. J. Cardiol.*, 6: 803, 1960.
2. Selkurt, E. E. Renal blood flow and renal clearance during hemorrhagic shock. *Am. J. Physiol.*, 145: 699, 1945.
3. Corday, E., Gold, H., de Vera, L., Williams, J. H. and Fields, J. Effect of the cardiac arrhythmias on the coronary circulation. *Ann. Int. Med.*, 50: 535, 1959.
4. King, S. E. and Baldwin, D. W. Production of renal ischemia and proteinuria in man by the adrenal medullary hormones. *Am. J. Med.*, 20: 217, 1956.
5. Fertig, H. H., Taylor, R. D., Corcoran, A. C. and Page, I. H. The renal manifestations of pheochromocytoma. *Ann. Int. Med.*, 35: 1358, 1951.
6. Bard, P. Medical Physiology, 10th edition, p. 226. St. Louis, 1956. C. V. Mosby Co.
7. Van Slyke, D. D. Effect of shock on the kidney. *Ann. Int. Med.*, 28: 701, 1948.
8. Van Slyke, D. D. Renal tubular failure of shock and nephritis. *Ann. Int. Med.*, 41: 709, 1954.
9. Corday, E. and Williams, J. H. Effect of shock and vasopressor drugs on the regional circulation of the brain, heart, kidney and liver. *Am. J. Med.*, 29: 228, 1960.
10. Sheehan, H. L. Symmetrical cortical necrosis of kidneys. *Brit. M. J.*, 2: 1327, 1950.
11. Oliver, J., MacDowell, M. and Tracy, A. Pathogenesis of acute renal failure associated with traumatic and toxic injury. *J. Clin. Invest.*, 30: 1305, 1951.
12. Golbraith, B. T. Lower nephron nephrosis associated with prolonged shock from ventricular tachycardia. *Am. Heart J.*, 42: 766, 1951.
13. Katz, A. M. Hemorrhagic duodenitis in myocardial infarction. *Ann. Int. Med.*, 51: 2: 212, 1959.
14. Si-Chun, M. and Levitan, R. Acute hemorrhagic necrosis of the gastro-intestinal tract. *New England J. Med.*, 263: 2: 59, 1960.
15. Glatzer, D. J. and Shaw, R. S. Massive bowel infarction: an autopsy study assessing the potentialities of reconstructive vascular surgery. *New England J. Med.*, 260: 4: 164, 1959.
16. Penner, A. and Bernheim, A. I. Acute postoperative enterocolitis. *Arch. Path.*, 27: 966, 1939.
17. Penner, A. and Bernheim, A. I. Acute postoperative esophageal, gastric, and duodenol ulceration. *Arch. Path.* 28: 129, 1939.
18. Penner, A. and Bernheim, A. I. Experimental production of digestive tract ulcers. *J. Exper. Med.*, 70: 453, 1939.
19. Greco, A. Sulla probabile natura dell'infarto intestinale sensa lesioni vascolari. *Gior. ital. chir.*, 3: 687, 1947.
20. Ende, N. Infarction of the bowel in cardiac failure. *New England J. Med.*, 258: 879, 1958.
21. Cone, T. E., Jr., Allen, M. S. and Pearson, H. A. Pheochromocytoma in children. *Pediatrics*, 19: 44, 1957.
22. Thorek, M. Occlusion mesenterica aguda: apoplezua intestinal por shock de intolerancia. *Rev. circ. Buenos Aires*, 20: 47, 1941.

23*A*. Corday, E., Irving, D. W., Gold, H. and Bernstein, H. B. Mesenteric vascular insufficiency: intestinal ischemia induced by remote circulatory disturbances. To be published.

23*B*. Editorial. Mesenteric vascular insufficiency. *J.A.M.A.*, 175: 335, 1961.

24. Grayson, J. and Swan, H. J. C. Action of adrenalin, noradrenalin, and dihydroergocornine on the colonic circulation. *Lancet*, 1: 988, 1950.
25. Deal, C. P., Jr. and Green, H. D. Comparison of changes in mesenteric resistance following splanchnic nerve stimulation with responses to epinephrine and norepinephrine. *Circulation Res.*, 4: 38, 1956.
26. Bearn, A. G., Billing, B. and Sherlock, S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *J. Physiol.*, 115: 430, 1951.

Partial Extracorporeal Circulation in Acute Heart Failure*

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HEART FAILURE IS an inability of the myocardium to maintain the blood requirements of the body during its varied physiologic functions [1–5] and, as Starling claimed,[6] represents an imbalance between the venous return and the cardiac output.[7–9] From this it follows that the treatment of acute heart failure should aim at providing the needed amount of blood for the tissues per unit of time.

The present day treatment of heart failure consists of drugs and measures which are intended to enable the heart to circulate the blood accumulated in the systemic veins. Compared to this endeavor, a recent approach proposes to circulate a varied amount of blood by means of a heart-lung machine until the myocardium recovers enough to withstand the work of supporting the entire circulation.

In order to accomplish this, extracorporeal circulation is instituted by diverting a variable percentage of venous return into a heart-lung machine and, after oxygenation, infusing it into the arterial system. This prevents a desired amount of blood from flowing into the heart and saves the work the myocardium would have done in order to propel this portion of circulating blood against arterial resistance.

The encouraging results of the pioneer investigators[10–12] in this field prompted us to investigate this problem in dogs with the hope that the information obtained thereby may be applicable to human cases. The present report summarizes the results on twenty-five dogs in which heart failure was produced and partial heart-lung bypass was used as the only therapeutic measure.

METHODS

Mongrel dogs, weighing 12 to 22 kg., were anesthetized with pentobarbital sodium (25 mg. per kg.) intravenously. A transthoracic sternum-splitting incision was made at the fifth intercostal space, with the animal air-ventilated through a cuffed tracheal tube by an intermittent positive pressure pump (Harvard). The pericardium was opened by a cross-like incision and its free edges were sewn to the chest wall to form a cradle to partially immobilize the heart. Pressures were registered via semirigid polyethylene tubes connected with Statham strain gauges, p23A and p23BB, and an Offner eight channel direct writing oscillograph recorder. Pressures were measured in the left atrium by a polyethylene catheter introduced through a segmental pulmonary vein, in the arterial system through a femoral artery, and in the left and right ventricle through purse-string controlled wounds in the lateral wall. During the entire operation, careful hemostasis was maintained. At this stage of the operation the dogs were heparinized (2.5 mg. per kg.).

The partial bypass was then instituted between major veins and a femoral artery by means of large plastic cannulas inserted into one or both femoral veins and a jugular vein (Fig. 1). After passing through the roller pumps the blood was raised into a Hyman-Abbott bag‡ which was suspended from a special post on a weight scale. This scale was connected to a strain gauge and calibrated accurately. By this arrangement the weight of the extracorporeal blood and, therefore, its volume could be controlled and recorded by an Offner direct writer. The priming volume of the bag ranged between 500 to 1000 ml. of blood. This priming blood was not cross-matched. After oxygenation in the bag, the blood was routed through the roller pump and returned through a short stainless steel cannula into the femoral artery. This arrangement of pump and bag allowed complete control over the inflow and outflow, either one of which could be independently adjusted according to the experimental needs.

Procedures to Induce Heart Failure: In the preliminary experiments pulmonary edema was induced as a

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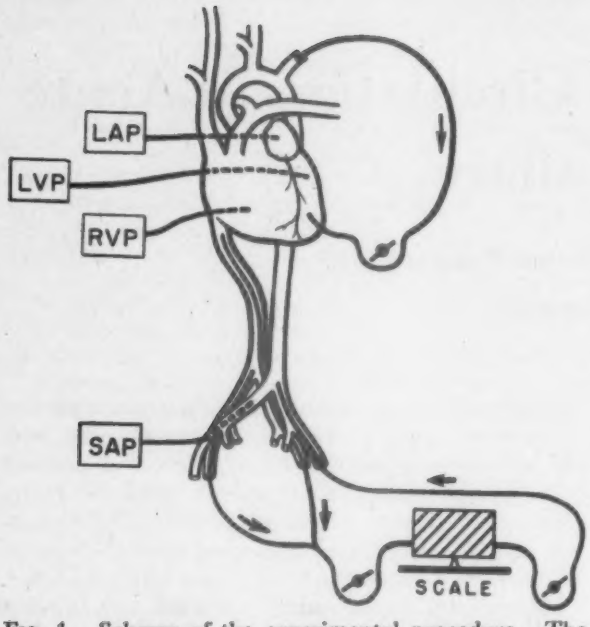

FIG. 1. Schema of the experimental procedure. The arrow and curved line from the left subclavian artery to the left ventricular cavity represents the shunt flow which was used to overload the left heart in the majority of cases. The circuit starting from the inferior vena cava via the femoral veins and ending in the abdominal aorta represents the extracorporeal circulation used for treatment of heart failure. LAP = left atrial pressure; LVP = left ventricular pressure; RVP = right ventricular pressure; SAP = systemic arterial pressure.

result of mitral insufficiency produced by section of the chordae tendineae or laceration of the mitral valve leaflets. Later it was found out that mitral incompetence could be produced by introducing a Tygon tube through the mitral orifice via the left atrial appendage.[13] This tube was perforated to allow regurgitation of the blood from the left ventricle into the left atrium during systole. This tube was obstructed by a tightly fitting obturator which could be adjusted to permit varying degrees of mitral insufficiency by pulling the obturator back, thereby opening more holes and increasing the regurgitation.

In approximately 60 per cent of the dogs the left atrial pressure rose significantly and pulmonary congestion followed the production of the mitral insufficiency. However, in the remaining dogs this procedure did not cause elevation of the left atrial and pulmonary pressures to levels comparable to those of pulmonary edema.[14,15] Such a rise could only be accomplished as a result of left ventricular failure. When the experiments were arranged to produce left heart failure, a pathophysiologic picture was obtained which corresponds to a frequent clinical emergency: left ventricular failure with pulmonary edema.

The left ventricular decompensation was produced by shunting blood from the left subclavian artery into the left ventricular cavity via a plastic cannula inserted through a stab wound at the apex. The flow

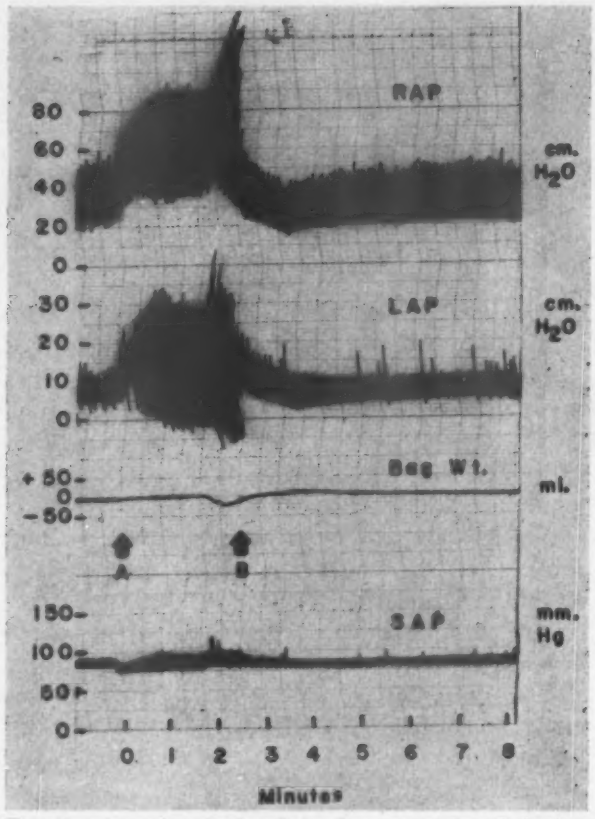

FIG. 2. At point A the shunt between left subclavian and left ventricular cavity was started; the marked rise of pressure in left and right ventricle is seen. Following the initiation of partial heart-lung bypass at point B, these pressures are reduced. RAP = right atrial pressure; LAP = left atrial pressure; Bag wt. = the weight of the plastic bag oxygenator indicating extracorporeal blood volume; SAP = peripheral arterial blood pressure.

in this circuit was controlled and maintained by a variable speed roller pump and ranged from 200 to 1200 ml. per minute. By manipulating the flow rate, the left ventricular diastolic and left atrial pressures could be increased to failure levels. In three dogs decompensation occurred only after one hour of overloading by this shunting system. In four others small branches of coronary arteries had to be ligated before heart failure occurred.

After the heart failure was initiated by one of these procedures or a combination of them, control pressures were recorded. The bypass circulation was initiated then between the caval veins and one of the femoral arteries (Fig. 1). The influence of various flow rates on the various chambers of the heart and peripheral arterial pressure was studied for periods up to three hours. Pressure contours, heart rate, strength of myocardial contraction and rhythm alterations were also studied.

RESULTS

Influence of Partial Heart-Lung Bypass on Heart Size and Cardiac Chamber Pressures: Heart fail-

TABLE I

Cardiac Chamber Pressures Before and During Partial Heart-Lung Bypass*

Case No.	Left Atrial Mean Pressure (mm. H_2O)			Right Ventricular Pressure (mm. H_2O)			Left Ventricular Pressure (mm. Hg)		
	Control Before Failure	Before Bypass	During Bypass	Control Before Failure	Before Bypass	During Bypass	Control Before Failure	Before Bypass	During Bypass
B_1	80	490	238	250	580	258	...	...	...
B_2	120	400	106	250	500	140	70	60	65
B_3	110	450	120	230	560	148	68	64	70
B_4	95	185	88	190	380	155	...	...	...
B_5	118	198	77	220	340	90	...	...	...
B_6	60	530	125	235	550/20	158	115	70/45	75
B_7	80	510	136	180	300/30	100	88	60/30	75
B_8	36	260	120	300	440/20	240/20	...	...	...
B_9	70	410	88	154/10	350/30	160/10	185	90/5	70
B_{10}	30	320	120	...	...	...	...	...	...
B_{11}	60	468	124	...	...	...	...	...	...
B_{12}	46	248	118	160	464	150	54	105	65
B_{13}	92	420	134	340	550	150	115	50/20	50
B_{14}	94	260	116	200	340	150	75	75	75
B_{15}	76	310	160	240	380/60	100/20	...	...	...
B_{16}	130	380	76	460	750	233	155	165	85
B_{17}	126	176	58	300	500/40	200	150	85	80
B_{18}	100	230	80	288	600/220	380/20	...	...	...
B_{19}	86	286	88	240/2	860/350	360	...	...	...
Mean	84.68	428.42	114.31	241	496	186	104	82	71

* Only the systolic levels of right and left ventricular pressures are recorded unless there were significant changes in diastolic pressures.

ure was induced in twenty-five dogs with the method described previously. When the left atrial pressure rose to levels indicative of failure (above 200 mm. H_2O),[14–17] and when the heart became dilated and its contractions weaker, the pump oxygenator was started with a flow rate of 20 to 25 ml. per kg. per minute. This was usually followed by a sudden drop in left ventricular diastolic, left atrial, right ventricular as well as systemic venous pressures and gradual reduction in the size of the heart with visible improvement in the contractions of the myocardium. In the meantime the color of the myocardium became pink and extrasystoles disappeared.

The pressure recordings of a typical experiment are illustrated in Figure 2. In this case laceration of the mitral valve did not produce a marked rise in the left atrial pressure. At point A the shunt between the left subclavian artery and the left ventricular cavity was started with a flow rate of 300 ml. per minute and later increased to 500 ml. per minute. As is seen in Figure 2, the right and left atrial pressures rose significantly. This rise in the pressures was followed by dilatation of the heart and numerous extrasystoles. At point B cardiopulmonary bypass was started with a flow rate of 300 ml. per minute. Immediately following this the left and right atrial pressures dropped. In a very short time these pressures were reduced to their original levels. The peripheral arterial blood pressure was maintained constant.

During the first few minutes of the bypass maintenance of the peripheral arterial pressure was rather difficult and needed careful balancing of inflow and outflow of the machine. This was only possible by keeping the blood volume of the dog at pre-bypass levels, and preventing unnecessary transfusion by monitoring the weight of the plastic bag oxygenator.

In some experiments flow rates of 25 to 50 ml. per kg. per minute did not control the heart failure. In these instances adequate decreases in the chamber pressures and reduction in the size of the heart were attained by increasing

TABLE II
Cardiac Chamber Pressures During and After Discontinuing Partial Heart-lung Bypass

Case No.	Peripheral Arterial Blood Pressure (mm. Hg)		Left Atrial Mean Pressure (mm. H_2O)		Right Ventricular Systolic Pressure (mm. H_2O)		Left Ventricular Systolic Pressure (mm. Hg)		Comments
	During Bypass	After Bypass	During Bypass	After Bypass	During Bypass	After Bypass	During Bypass	After Bypass	
C_1	70/35	85/45	80	80	50	320	50	85	Heart was able to support the circulation after discontinuation of bypass.
C_2	108/80	105/60	52	48	300	260	...	...	Heart was able to support the circulation after discontinuation of bypass.
C_3	85/60	110/65	36	36	50	350	75	115	Left atrial pressure rose for a short while upon discontinuation of bypass. Later, heart became compensated.
D_1	60/35	55/30	74	220	160/5	580/60	64	74/10	Upon discontinuation of bypass, heart failure returned.
D_2	65/35	35/20	60	392	70/10	25/20	60/35	45/25	Upon discontinuation of bypass, heart enlarged, cardiac chamber pressures rose and later ventricular fibrillation set in.

the flow rate gradually to higher levels.

The results of nineteen experiments are summarized in Table I. The control mean pressures in the *left atrium* ranged from 30 to 120 mm. H_2O with an over-all mean of 84 mm. H_2O. When failure was induced these pressures rose to levels ranging from 170 to 510 mm. H_2O. These figures compare favorably with those reported.[18–20] Application of extracorporeal circulation with an appropriate flow rate, which was different in each case, reduced these pressures to levels comparable to those of controls.

The response of pressures in the *right ventricle* was in the same direction as that of the left atrium. Here the control systolic pressures ranged from 154 to 460 mm. H_2O, with an average of 241 mm. H_2O. When failure was instituted the right ventricular systolic pressure ranged from 300 to 860 mm. H_2O, the mean being 496 mm. H_2O. The partial heart-lung bypass caused a significant reduction in these pressures and was followed by improvement of the circulation (Table I).

The *left ventricular* pressure was measured in ten cases and the diastolic pressure was elevated in four cases (Table I, Cases B_6, B_7, B_9 and B_{13}) while in the rest it was not altered significantly. The left ventricular systolic pressure either went up, stayed the same or fell. All these abnormal pressures tended to return to their original values when the heart-lung machine was operated.

In some cases cardiac failure was alleviated by a short run of the bypass. However, immediately after discontinuation of the perfusion, the heart returned again to its decompensated state. In these instances additional bypass of twenty to thirty minutes frequently enabled the heart to carry the circulation without any sign of failure when the perfusion was stopped for the second time.

Table II shows the typical course of events upon *discontinuation of partial extracorporeal circulation*. In the first two cases (C_1 and C_2) the heart could support the circulation when the pump was turned off, individual cardiac chamber pressures remaining the same as during perfusion. In the third case (C_3), however, the left atrial mean pressure rose to 140 mm. H_2O upon discontinuation of the partial bypass as the heart showed signs of failure and later gradually came down as the heart recovered.

In the last two cases in Table II, cardiac failure returned upon discontinuation of the

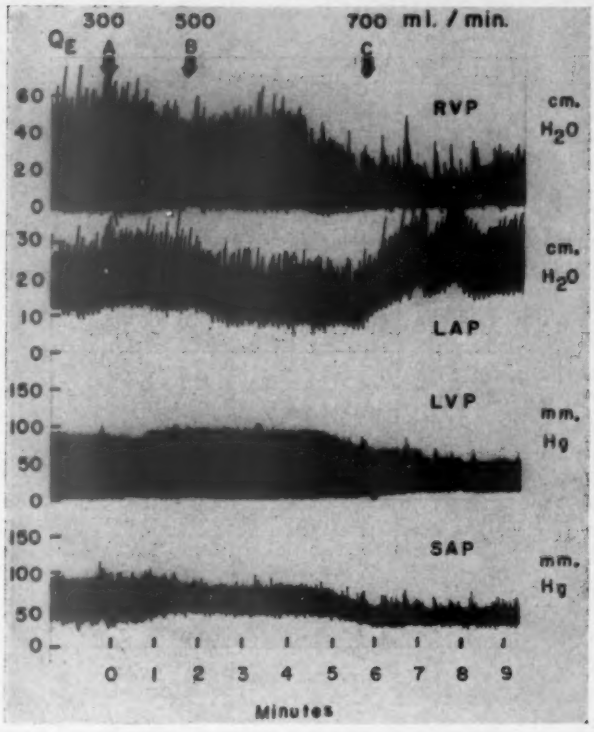

FIG. 3. Effects of increasing extracorporeal flow rate on cardiac chamber pressures. Heart failure is evident at the beginning of the recording where the left atrial pressure is 300/120 mm. H_2O and diastolic left ventricular pressure, 5 mm. Hg. At point A the partial heart-lung bypass is started with a flow rate of 20 ml. per kg. per minute, which causes some reduction in left atrial and right ventricular pressures. This drop is more obvious with 33 ml. per kg. per minute of bypass flow (point B). However, when the flow rate is increased to 46 ml. per kg. per minute (point C), the peripheral arterial and left ventricular systolic pressures drop, left ventricular diastolic pressure rises to 15 mm. Hg and left atrial pressure also rises. Abbreviations as in Figure 1.

partial extracorporeal circulation. In Case D_1 when the pump oxygenator was stopped, the left atrial mean pressure rose to 220 mm. H_2O and right ventricular pressure to 580/60 mm. H_2O. In this case additional bypass of thirty minutes was followed by compensation when the heart-lung machine was stopped for the second time. In case D_2 decompensation followed the discontinuation of bypass and ended in ventricular fibrillation.

Optimal Extracorporeal Flow Rate: In most of the cases, after the failure was produced, bypass was started with a flow rate of 20 to 25 ml. per kg. per minute. This was usually followed by a significant improvement in the circulation. Increasing the flow rate to 50 ml. per kg. per minute reduced the elevated pressures further. A higher flow rate, however, in some instances caused return of heart failure with all of its manifestations, as is demonstrated in Figure 3. In this dog mitral insufficiency caused heart failure without the use of the subclavian artery-left ventricle shunt. Starting the partial heart-lung bypass with a flow rate of 300 ml. per minute (20 ml. per kg. per minute) reduced the right ventricular pressure slightly. The circulation of the dog was significantly improved when the flow rate was increased to 500 ml. per minute (33 ml. per kg. per minute). However, return of failure (manifested by marked enlargement of the heart, reduction of systolic and elevation of diastolic pressure in the left ventricle, a marked rise in left atrial pressure, irregularities of rhythm and visible reduction of the contractile force) was observed when the flow was increased to 700 ml. per minute (46 ml. per kg. per minute).

Influence of Bypass on Severe Hypotension: In sixteen of twenty-five dogs severe hypotension occurred late in the course of the experiment. In these instances it was possible to maintain their peripheral arterial pressures at near normal levels by perfusing the animal with an appropriate flow rate. Data of these experiments are summarized in Table III.

A typical case is illustrated in Figure 4. This dog had been in failure and placed on bypass for several hours. During this time the blood pressure was maintained around 90/65 mm. Hg. Suddenly it was observed that the general condition deteriorated, failure returned and blood pressure dropped to 50/32 mm. Hg, despite the fact that the heart-lung machine was circulating the same amount of blood per minute as before. At this time the pump-oxygenator was turned off. As can be seen from the figure the blood pressure dropped to 30/15 mm. Hg. Starting the bypass with a flow rate of 300 ml. per minute caused a gradual rise of blood pressure to 60/35 mm. Hg and a flow rate of 700 ml. per minute, to 75/58 mm. Hg. The fact that this rise in blood pressure was not due to a spontaneous recovery is proved by return of severe hypotension following discontinuation of the perfusion.

In numerous cases it was possible to maintain a normal blood pressure with assisted circulation until the animal became able to sustain its own pressure at physiologic levels without further help. In one case the blood pressure dropped to 20/8 mm. Hg. Partial heart-lung bypass with a flow rate of 300 ml. per minute (20 ml. per kg. per minute) brought the blood pressure to 55/35 mm. Hg. A gradual

TABLE III
Shock

Case No.	Peripheral Arterial Blood Pressure (mm. Hg) (flow rates, 0–1200 ml. per minute)							Pump Off
	Control	300	500	700	840	1000	1200	
A_1	32/18	52/30	58/40	70/48	78/52	80/55	80/55	...
A_2	20/12	85/60	115/70	125/80	140/88	150/96	...	...
A_3	55/28	58/28	60/32	70/50	110/80	110/94	132/96	...
A_4	20/10	52/43	65/45	65/48	70/50	90/63	...	...
A_5	15/5	25/20	70/45	60/45	58/45	55/35	...	...
A_6	20/15	25/18	68/43	80/52	80/55	80/55	...	94/58
A_7	35/10	50/25	64/32	78/40	90/43	95/40	...	90/38
A_8	25/15	55/35	65/40	76/52	84/60	90/62	100/65	108/80
A_9	30/15	56/40	75/55	88/55	104/60	106/66	...	40/20
A_{10}	15/10	55/40	58/35	60/30	65/38	80/38	80/45	75/50
A_{11}	50/26	70/42	75/48	115/55	118/64	120/70	...	75/40
A_{12}	30/26	32/20	35/20	40/30	50/35	70/45	75/50	75/50
A_{13}	20/10	50/35	65/40	70/45	132/68	130/98	...	75/50
A_{14}	17/8	25/15	45/25	70/45	70/55	80/65	100/75	15/8
A_{15}	35/15	42/22	50/35	90/70	130/86	140/100	...	98/64
A_{16}	25/15	35/20	50/30	62/44	70/48	75/50	...	...
Mean	27/14	47/30	63/39	76/49	90/57	97/64	77/64	75/45

rise in the extracorporeal flow rate was closely paralleled by a rising blood pressure. After a perfusion of thirty-five minutes this dog was able to maintain its own blood pressure at physiologic levels without further help of the heart-lung machine.

It is important to note that in some cases with severe hypotension it was possible to increase the peripheral arterial blood pressure significantly without transfusion during the bypass procedure. However, in the majority of the instances a small amount of transfusion (20 to 30 ml.) was needed in order to increase the rate of extracorporeal blood flow from one step to another. In some cases in which the venous return was adequate to increase the flow rate there was no need to increase the blood volume of the dog to raise the blood pressure. The total amount of transfusion usually was about 100 ml. and enabled us to increase the rate of flow as high as 120 ml. per kg. per minute. This amount of blood was sometimes recovered when the bypass was stopped.

COMMENTS

Acute heart failure, whether it involves only the left or right heart or both sides combined, is a hemodynamic catastrophe frequently resulting in death because of pulmonary edema. Its treatment at present consists of drugs and measures attempting to enable the heart to handle the work required for adequate circulation. The phlebotomy, practiced even by early physicians, on the other hand, showed the benefits of reducing the work of the myocardium in such emergency conditions. It is well known, however, that removal of a large amount of blood from patients in severe heart failure often induces shock. Some of these patients are already hypotensive when they arrive at the hospital. Therefore, their clinical picture even though it may have started as a hypervolemic heart failure can no longer be benefited from exsanguination.

This important consideration stimulated a great deal of research in the last two decades and intra-arterial transfusion was introduced as a treatment for such cases.[21–25] Some investigators went so far as considering intra-arterial transfusion as a secondary heart[25] in cases of severe shock. It was shown by several investigators[25,26] and recently confirmed by Miller et al.[27] that the intra-arterially transfused blood reaches the coronary and cerebral vessels in a few seconds instead of pooling in the venous system as is the tendency if blood is transfused intravenously. Proper filling of the coronary arteries requires considerable arterial pressure. Intra-arterial perfusion elevates the peripheral arterial pressure; therefore, the im-

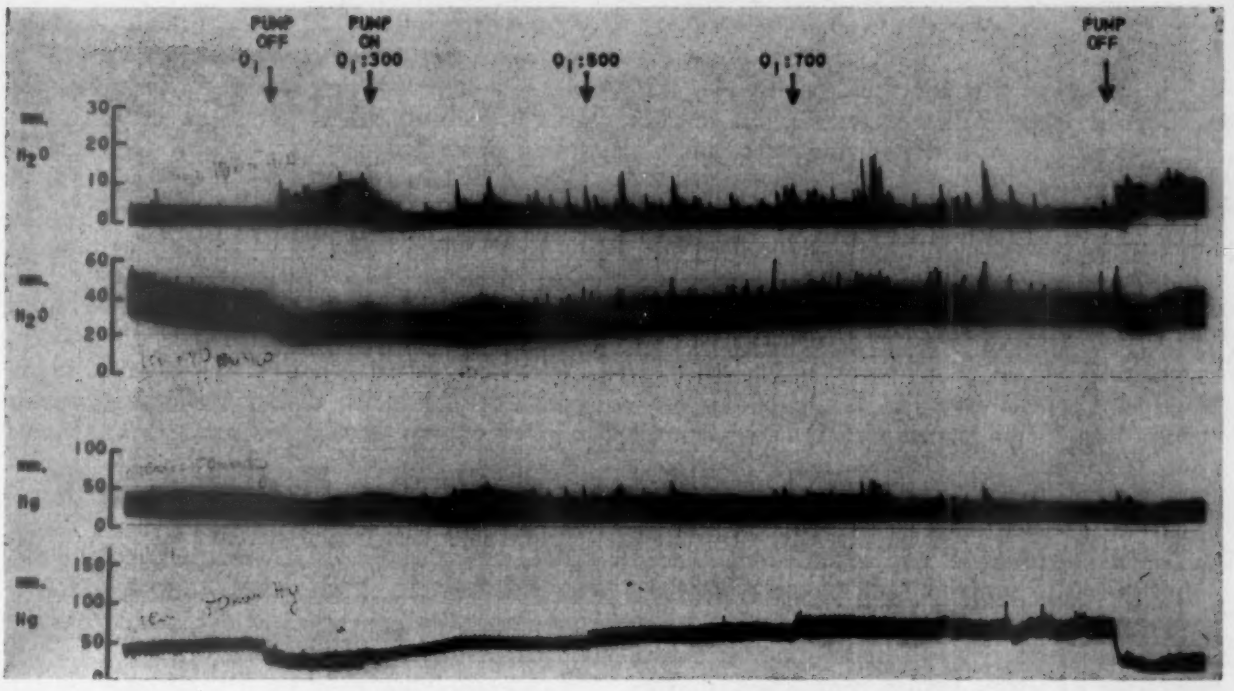

FIG. 4. Experiment demonstrating effect of bypass on hypotension. Peripheral arterial pressure: arterial blood pressure in this dog dropped to 35/18 mm. Hg. Starting partial bypass with a total flow rate of 300 ml. per minute brought the blood pressure to 60/42 mm. Hg. By increasing the flow rate of the machine gradually to 700 ml. per minute, it was possible to bring the systemic arterial blood pressure to 85/60 mm. Hg. When the pump was stopped the blood pressure dropped again to 35/20 mm. Hg. The upper channel recording is the right ventricular pressure; second channel, the right atrial pressure; third, the left ventricular; and the bottom channel is the peripheral arterial blood pressure.

provement in oxygenation of the myocardium which results may be adequate to restore the myocardial function if no irreversible damage has occurred.[27] It has recently been shown by Storli et al.[28] that the impaired coronary circulation of dogs in right heart failure is restored to normal limits following partial heart-lung bypass.

Even though introduced with these considerations, intra-arterial transfusion actually found very little application because of the fact that the transfused amount of blood increases the work of the heart. This increased work may not be tolerated by the myocardium and may precipitate decompensation. This is in agreement with Maloney et al.[29] whose experiments showed no difference in results of cases transfused intra-arterially or intravenously. The experience gained from the use of the two methods of transfusion pointed to the need of better ways of helping the failing heart mechanically.

Extracorporeal circulation represents a combination of the two methods discussed above. Actually it is a continuous venous exsanguination combined with a continuous intra-arterial transfusion. A varied percentage of blood never reaches the heart and is circulated by the pump; therefore, it is assumed that the "myocardial work" is much less under bypass conditions.[30]

The potential advantages of the heart-lung bypass was appreciated early in the development of the heart-lung machines. Several investigators pioneered in the application of this method to the treatment of numerous heart diseases varying from cor pulmonale to myocardial infarction.[10-12,31] The success attained by these investigators suggested that accumulation of knowledge on the influence of partial extracorporeal circulation on the failing circulation may make its use possible in clinical medicine. The knowledge needed in order to accomplish this goal is not available at the present time.[30,32] Even though it was shown by Galletti and Salisbury[33] and confirmed by Wyman et al.[34] that following initiation of partial heart-lung bypass the heart rate slows down and the cardiac output can be reduced by the amount circulated through the pump-oxygenator, much of the hemodynamic as well as metabolic effects of incorporating

a pump into the circulation remains unknown. It is logical that elucidation of these problems will help outline the indications as well as the contraindications of this procedure and enable one to use this method judiciously in clinical practice.

Criteria for Heart Failure: In pursuing these experiments we became aware of the fact that there is no standardized and uniformly accepted method of producing heart failure. Therefore, it was necessary to use the widely accepted criteria for diagnosis of myocardial failure and to consider the details of the procedure of inducing decompensation of secondary importance.[7,15-18,35,36]

Most investigators accept dilatation of the heart with elevation of ventricular diastolic and atrial pressures as indicative of heart failure. It can be seen from Table 1 that left atrial pressure rose to very high levels, 428 mm. H_2O as an over-all mean. This figure compares favorably with the figures mentioned in the literature as indicative of heart failure.[15-18] Ventricular diastolic pressures were also found high in cases where they were measured. These impressive elevations of pressures were accompanied by marked enlargement of the heart, rhythm alterations and visible reduction of contractile power of the myocardium.

Treatment of Acute Heart Failure: It is apparent from our results that acute heart failure can be improved by partial heart-lung bypass. When the heart is dilated and accompanied by increased atrial and ventricular pressures, the initiation of the partial heart-lung bypass reduces the size of the heart and brings the elevated pressures to normal levels. The fact that improvement was not temporary is proved by the observation that after stopping the extracorporeal circulation following a period of bypass the majority of cases remained in compensation. In some cases, however, failure returned when the bypass was stopped. Most of the animals of this last group were again placed on partial extracorporeal circulation during which time the failure was controlled. It was noted that the recovery of the myocardium was related to the total bypass time; dogs which had failure following ten to twenty minutes of partial perfusion did well if they were perfused longer.

Dogliotti[10] reported a case in which a patient suddenly went into circulatory failure while a mediastinal operation was being performed, but responded favorably to immediate partial venous-arterial bypass. This patient's general condition improved, heart failure disappeared and blood pressure returned to normal limits after twenty minutes of the procedure. He stated that the patient was well two months after the operation.

It can be concluded from our results and substantiated by the case history reported by Dogliotti that acute heart failure may be alleviated by the use of partial extracorporeal circulation. In instances in which the conventional therapy does not bring forth improvement, compensation can be achieved by partial heart-lung bypass. If this is continued for a sufficient period of time the heart may be able to support the circulation after partial extracorporeal circulation is stopped.

Treatment of Chronic Heart Failure: Reports of Helmsworth,[11] Stuckey,[12] Dickson[37] and their associates are concerned with chronic cardiac or cardiopulmonary failure due to a variety of causes. They have shown that the patients can be improved significantly as soon as the bypass procedure is begun. However, this improvement may not be permanent. Whether future research will reveal information which may enable bringing permanent improvement to these chronic failure cases is yet to be seen. Stuckey and his collaborators,[12] using medical treatment in combination with partial extracorporeal circulation, have shown that there is no question that an acute exacerbation of chronic heart failure can be controlled by this method.

Complications: It is likely that further research and clinical experience with extracorporeal circulation in heart failure will expose complications which cannot be foretold. It is certain, however, that this method of treatment is not to be used indiscriminately. This conclusion is suggested by the work of Patt et al. who used venoarterial pumping in normal dogs and dogs with coronary occlusion.[38] Salisbury has shown that vein to artery perfusion was deleterious or had no effect on left ventricular heart failure; however, it was beneficial in right ventricular failure.[39] Our experiments have shown that some extracorporeal flow rates are deleterious to the subject. This is seen in Figure 3; high rates of output of the pump-oxygenator caused a deterioration of the general condition and return of circulatory failure in the dog. The cause and hemodynamics of this phenomenon are under investigation at the present time.

Effect on Hypotension and Shock: An important by-product of these experiments was the observation that peripheral arterial blood pressure could be maintained at normal levels for as long as desired. In some cases where shock returned following discontinuation of partial extracorporeal circulation longer periods of bypass enabled the animal to sustain its blood pressure at physiologic levels when the perfusion was stopped for the second time.

This observation raised the question whether the blood pressure could be maintained at desired levels in severe shock of various etiologies and whether metabolic consequences of long term bypass would respond favorably to this procedure. These problems are being investigated at the present time.

Several investigators in the past have stated that they were able to raise the blood pressure to near normal levels by increasing the flow rate of the heart-lung machine during complete cardiopulmonary bypass.[40–45] Kuhn et al.[45] recently have proposed obstructing the lower portion of the aorta by a balloon, thereby increasing the resistance to blood flow, meanwhile perfusing the dog by a heart-lung machine.

Summary

Acute heart failure was produced in twenty-five dogs by a combination of mitral insufficiency, overtransfusion and ligation of small branches of coronary arteries in order to study the effects of partial extracorporeal circulation. It was found that the failing heart returned to compensation following short periods of partial perfusion. In some other animals the failure was more profound and longer periods of partial perfusion were necessary before their hearts could maintain compensation.

There was an optimal flow rate which most benefited the failing heart. This was different for each dog and varied under different conditions in the same animal.

Severe persistent hypotension set in after several hours of experimentation in several dogs, but the blood pressure of these animals was restored to normal by means of partial extracorporeal circulation with appropriate flow rates.

References

1. Dock, W. Heart failure. The relation of symptoms and signs to its severity and duration. *Ann. Int. Med.*, 29: 11, 1948.
2. Huckabee, W., Casten, G. and Harrison, T. R. Experimental hypervolemic heart failure: Its bearing on certain general principles of heart failure. *Circulation*, 1: 343, 1950.
3. Visscher, M. B. Heart failure. *Mod. Concepts Cardiovas. Dis.*, 14: No. 8 and 9, 1945.
4. Harrison, T. R., Friedman, B. and Resnik, H. Mechanism of acute experimental heart failure. *Arch. Int. Med.*, 57: 927, 1936.
5. Cournand, A. A discussion of the concept of cardiac failure in the light of recent physiologic studies in man. *Ann. Int. Med.*, 37: 649, 1952.
6. Starling, E. H. The Linacre Lecture on the Law of the Heart. London, 1918. Longmans, Green & Co.
7. McGuire, J., Shore, R., Haunstein, V. and Goldman, F. Relation of cardiac output to congestive heart failure. *Arch. Int. Med.*, 63: 290, 1939.
8. Fishberg, A. M. Heart Failure, 2nd ed., p. 27. Philadelphia, 1940. Lea & Febiger.
9. Friedberg, K. C. Diseases of the Heart, 2nd ed., pp. 161, 180. Philadelphia, 1956. W. B. Saunders Co.
10. Dogliotti, M. A. Clinical use of the artificial circulation with a note on intra-arterial transfusion. *Bull. Johns Hopkins Hosp.*, 90: 131, 1952.
11. Helmsworth, J. A., Clark, L. C., Kaplan, S. and Sherman, R. T. Clinical use of extracorporeal oxygenation with oxygenator pump. *J.A.M.A.*, 150: 451, 1952.
12. Stuckey, J. H., Newman, M. M., Dennis, C., Berg, E. H., Goodman, S. E., Fries, C. C., Karlson, K. E., Blumenfeld, M., Weitzner, S. W., Binder, L. S. and Winston, A. The use of the heart-lung machine in selected cases of acute myocardial infarction. *S. Forum*, 8: 342, 1957.
13. Welch, G. H., Jr., Braunwald, E. and Sarnoff, S. J. Hemodynamic effects of quantitatively varied experimental aortic regurgitation. *Circulation Res.*, 5: 546, 1957.
14. Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H. and Baldwin, E. DeF. Pressure of blood in the right auricle in animals and in man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.
15. Richards, D. W., Jr., Cournand, A., Darling, R. C. and Gillespie, W. H. Pressure in the right auricle in man, in normal subjects and in patients with congestive heart failure. *Tr. A. Am. Physicians*, 56: 218, 1941.
16. Luisada, A. A. Heart, p. 137. Baltimore, 1948. Williams & Wilkins Co.
17. Richards, D. W., Jr. Contributions of right heart catheterization to the physiology of congestive heart failure. *Am. J. Med.*, 3: 434, 1947.
18. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S. and Richards, D. W., Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. *J. Clin. Invest.*, 25: 639, 1946.
19. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonnson, B. Diagnosis of Congenital Heart Disease, p. 119. Chicago, 1959. Yearbook Publishers.
20. Cournand, A., Baldwin, J. S. and Himmelstein, A.

Cardiac Catheterization in Congenital Heart Disease, pp. 20, 75. New York, 1949. The Commonwealth Fund.

21. Berman, E. F. and Akman, L. C. Intra-arterial transfusion in the treatment of shock resulting from coronary occlusion. *Am. Heart J.*, 43: 264, 1952.
22. Silber, E. N., Levin, B. D., Becher, G. H. and Levy, R. C. Treatment of shock in recent myocardial infarction by intraarterial transfusion. *J.A.M.A.*, 147: 1626, 1951.
23. Jones, P. G., Davis, J. H., Jr., Hubay, C. A. and Holden, W. D. Physiologic mechanisms of intra-arterial transfusion. *Surgery*, 27: 189, 1950.
24. Glasser, O. and Page, I. H. Experimental hemorrhagic shock; a study of its production and treatment. *Am. J. Physiol.*, 154: 297, 1948.
25. Page, I. H. Participation of the heart in shock. *Mod. Concepts Cardiovas. Dis.*, 16: No. 9, 1947.
26 Miller, J. A., Jr. and Westin, B. Venous and arterial contrast radiography in stillborn fetuses; implications in neonatal resuscitation. *Surgery*, 46: 1140, 1959.
27. Miller, J. A., Jr. Personal communication.
28. Storli, E. A., Connolly, J. E., Bacaner, M. and Bruns, D. L. The relationship of coronary blood flow to the effectiveness of mechanical support of the circulation in acute heart failure. *S. Forum*, 11: 214, 1960.
29. Maloney, J. V., Jr., Smythe, C. McC., Gilmore, J. P. and Handford, S. W. Intra-arterial and intravenous transfusion. A controlled study of their effectiveness in the treatment of experimental hemorrhagic shock. *Surg. Gynec. & Obst.*, 97: 529, 1953.
30. Rutherford, R. B. and Swan, H. Experimental partial perfusion. *S. Forum*, 11: 212, 1960.
31. Rygg, I. H. Personal communication.
32. Thrower, W. B., Veith, F. J., Lunzer, S. and Harken, D. E. The effect of partial extracorporeal bypass on sodium excretion in normal dogs and in those with heart failure. *Surg. Gynec. & Obst.*, 110: 19, 1960.
33. Galletti, P. M. and Salisbury, P. F. Partial extracorporeal circulation in closed chest dogs. *J. Appl. Physiol.*, 14: 684, 1959.
34. Wyman, M. G., Weil, M. H. and Blankenhorn, D. H. Partial cardiopulmonary bypass utilizing selective veno-arterial perfusion. *J. Clin. Invest.*, 38: 1056, 1959.
35. Rushmer, R. F. Cardiac Diagnosis. A Physiologic Approach, p. 135. Philadelphia, 1956. W. B. Saunders Co.
36. Wiggers, C. J. Dynamics of ventricular contraction under abnormal conditions. *Circulation*, 5: 321, 1952.
37. Dickson, J. F., iii, Hamer, N. A. J. and Dow, J. W. Veno-arterial pumping for relief of intractable cardiac failure in man. *Arch. Surg.*, 78: 418, 1959.
38. Patt, H. A., Clift, J. V., Loh, P. B., Roa, J. C., Wexler, J. and Seligman, A. M. Veno-arterial pumping in normal dogs and dogs with coronary occlusion. *J. Thoracic & Cardiovas. Surg.*, 39: 464, 1960.
39. Salisbury, P. F., Cross, C. E., Rieben, P. A. and Lewin, R. J. Comparison of two types of mechanical assistance in experimental heart failure. *Circulation Res.*, 8: 431, 1960.
40. Dodrill, F. D., Marshall, N., Nyboar, J., Hughes, C. H., Derbyshire, A. J. and Stearns, A. B. The use of heart-lung apparatus in human cardiac surgery. *J. Thoracic Surg.*, 33: 60, 1957.
41. Salisbury, P. F., Bor, N., Lewin, R. J. and Rieben, P. A. Effects of partial and of total heart-lung bypass on the heart. *J. Appl. Physiol.*, 14: 458, 1959.
42. Clowes, G. H. A., Jr., Neville, W. E., Sabga, G. and Shibota, Y. The relationship of oxygen consumption, perfusion rate and temperature to the acidosis associated with cardiopulmonary circulatory bypass. *Surgery*, 44: 220, 1958.
43. Lillehei, C. W., Gott, V. L., DeWall, R. A. and Varco, R. L. The surgical treatment of stenotic or regurgitant lesions of the mitral and aortic valves by direct vision utilizing pump oxygenator. *J. Thoracic Surg.*, 35: 154, 1958.
44. Salisbury, P. F., Bor, N., Lewin, R. J., Rieben, P. A. and Cross, C. E. Effects of partial and of total heart-lung bypass on the circulation. *Trans. Am. Soc. Art. Int. Organs*, 5: 197, 1959.
45. Kuhn, L. A., Gruber, F. L., Frankel, A. and Kupfer, S. Hemodynamic effects of extracorporeal circulation in closed chest animals and in those with myocardial infarction with shock. *Circulation Res.*, 8: 199, 1960.

New Methods

High Frequency Phonocardiography*

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MOST CLINICAL PHONOCARDIOGRAMS have been recorded so far in either the medium-low (60 to 150 c.p.s.) or the medium-high (150 to 300 c.p.s.) frequency range. Leatham[1] was one of the first to call attention to the fact that tracings recorded in the medium-high frequency range reveal with special clarity acoustic phenomena of clinical importance (clicks, snaps, components of either the first or second sound, rubs, soft blowing murmurs). Other authors[2-5] also recorded clinical tracings in the medium-high and even the high frequency range. However, their tracings were hampered by the fact that until recently most apparatus had a limited high frequency response characteristic.

Clear tracings in the high frequency range (above 300 c.p.s.) can be recorded by using the new standardized and calibrated apparatus† described previously.[6,7] Hence, a systematic study of the high frequency vibrations created by the normal or abnormal heart was made possible.

METHOD AND MATERIAL

This study was made by means of the new phonocardiograph of Luisada and Zalter.[6,7] This is based on a Krohn-Hite band pass filter with a slope of −24 decibels per octave at each end of the band (Fig. 1). The present study made use of two galvanometers, the No. 1100 and the No. 3000, both having a linear frequency response up to two-thirds of their maximal response (respectively 700 and 2000 c.p.s.).

Amplification: The problem of preventing two possible sources of artifacts when using great amplification was solved in the following ways:

(1) An additional variable filter with a slope of −12 decibels per octave was placed between preamplifier and band pass filter. This prevented overloading of the band pass filter by low frequency vibrations and resulted in an over-all slope of up to −36 decibels per octave (Fig. 1).

(2) Care was taken to give only a moderate increase of amplification in the preamplifier (not more than 30 decibels) and a greater amplification in the postamplifier. Special tests were performed with a signal generator creating a sine wave at 60 or 120 c.p.s. with a magnitude comparable to that of the human heart sounds. These tests revealed that no transients or overtones were created by the system.‡

Frequency Bands: According to a previous suggestion,[9,10] six frequency bands were usually recorded as follows: 30-60, 60-120, 120-240, 240-480, 500-1000 and 1000-2000. In the present study, only the last two bands plus occasional higher bands (1500-2000 or 2000-2500) were considered. However, comparison was also made between the vibrations recorded in these bands and those of lower frequency bands.

Method of Recording: The apparatus recorded the following tracings simultaneously:

(1) An electrocardiogram.

(2) A "stethoscopic" tracing§ (by means of a Sanborn twin-beam connected with one of the six channels of the new phonocardiograph).

(3) A filtered tracing in the desired octave band.

(4) Occasionally, a suprasternal pulse tracing, an ultralow frequency tracing of the apex, or a low

† This apparatus was built with the collaboration of the Altec-Lansing Corp., Pasadena, California, the Krohn-Hite Co., Boston, Massachusetts, and the Electronics Limited Co., London, England. The preliminary studies involved in its construction were partly made by H. Hodara, M.S.; further refinements and calibration were contributed by G. Gabriel, M.S. in this laboratory.

‡ These tests were performed by Mr. G. Gabriel, M.S. of the Illinois Institute of Technology.

§ This tracing is obtained through the use of a dynamic microphone which has a response equal to a rise of 6 decibels per octave with increase in frequency, and a nearly flat response of the amplifier.

* From the Division of Cardiology of The Chicago Medical School and Mount Sinai Hospital. This study was made, under the tenure by Dr. Luisada of an Under graduate and a Graduate Training Grant of the National Heart Institute, U. S. Public Health Service, and with the aid of Grant H-3785 by the National Heart Institute.

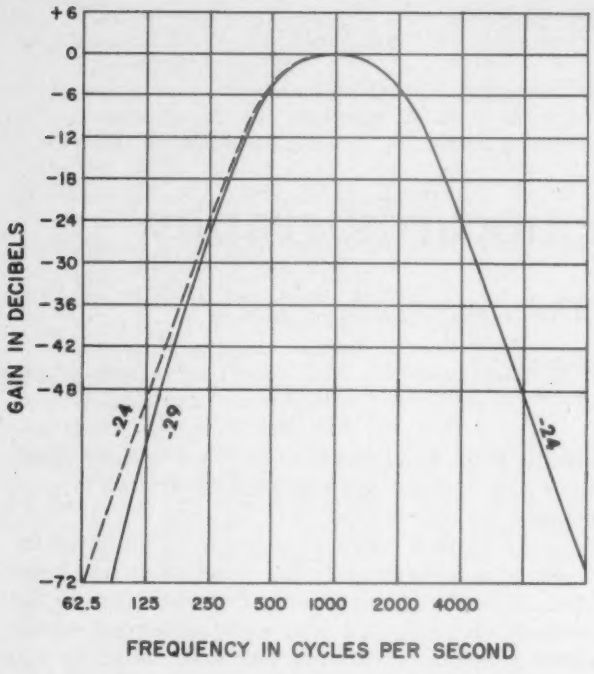

FIG. 1. Characteristics of the band pass filter combined with an RC high pass filter (continuous line). The dotted line represents the high pass section of the band pass filter alone. The RC filter is set at one quarter of the low cut off of the band pass filter resulting in a slope of −29 decibels per octave between −12 and −72 decibels.

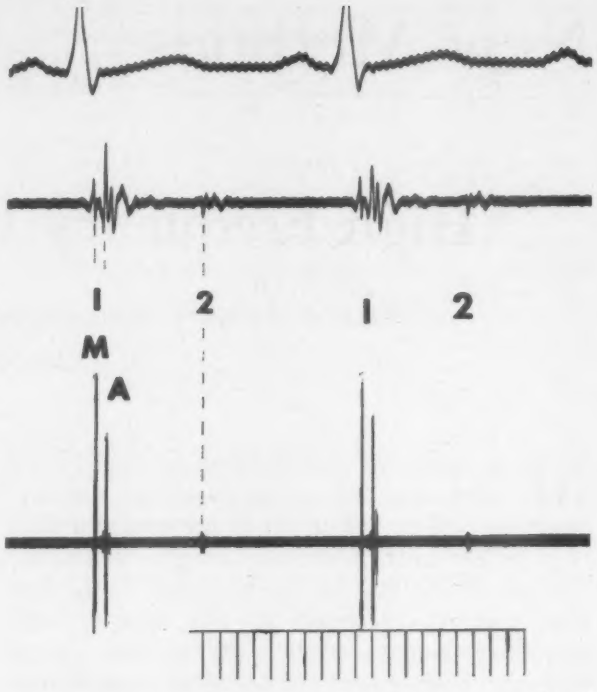

FIG. 2. Normal man of twenty-one years. Tracings recorded at the midprecordium. *From above:* electrocardiogram; "stethoscopic" phono; filtered phono (band 1000-2000 cycles per second). The first sound has two groups of vibrations while the second is represented only by a small vibration. Time lines indicate 0.04 second (film speed = 80 mm./second in this, as well as in the subsequent tracings). M = mitral component; A = aortic component of first sound. Notations are made according to previously published suggestions (*Am. J. Cardiol.*, 4: 40, 1959[6]).

frequency acceleration tracing of the midprecordium were also recorded for the identification of certain vibrations.

The microphone was applied on the skin of the precordium by means of a suction cup. A small stopcock, closed soon after the application, prevented the establishment of a positive air pressure in the cup. The Altec (capacitance) microphone was about 1 cm. from the skin and air transmission carried the vibrations from the skin to the microphone. A side connection from the same funnel carried air vibrations to a dynamic microphone for the "stethoscopic" tracings. Most of the tracings were recorded over the third and fourth intercostal spaces with the rim of the cup at 2 cm. from the left sternal margin. Most of the significant vibrations of the heart are recorded in this central area, called the "midprecordium." Some tracings, however, were recorded in the fourth, fifth or sixth intercostal spaces (apex), in the second left (pulmonic area) or in the second right intercostal space (aortic area). The patient was instructed to hold his breath in expiration after a small inspiration and the tracings were always recorded in apnea.

Following the recording of the phonocardiogram in the lower frequency bands, the higher bands were explored. The degree of amplification was increased normally in order to clearly bring out the vibrations of the heart sounds (or of high pitched murmurs, if the sounds were poorly visible). Usually, tracings were recorded until the heart sounds or murmurs disappeared or were overshadowed by "noise." In certain cases, an intermediate half-octave band was recorded. For example, occasionally a band 750-1000 or 1000-1500 clearly revealed the sounds when a full band was unable to do so.

The degree of amplification in decibels was usually noted.

Case Material: The study was made in forty-seven cases as follows:

Five subjects without evidence of heart disease.
Ten cases of pure or predominant mitral stenosis.
Eight cases of pure or predominant aortic stenosis.
Three cases of pure or predominant mitral insufficiency.
Four cases of pure or predominant aortic insufficiency.
One case of hypertensive heart disease.
One case of chronic cor pulmonale.
Six cases of subacute or chronic myocarditis.
Three cases of congenital heart disease.
Two cases of pericarditis.
Four cases with murmurs in which no final diagnosis was made.

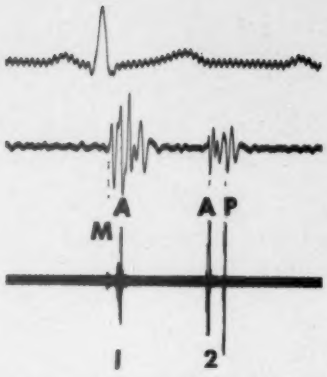

FIG. 3. Borderline case. Twelve year old boy. Tracings recorded at the midprecordium. *From above:* electrocardiogram, "stethoscopic" phono, filtered phono (band 600-800 cycles per second). The first sound shows two groups of vibrations; the second group (A) is larger than the first group (M). The second sound also shows two groups of vibrations, A (aortic) and P (pulmonic).

RESULTS

GENERAL FINDINGS

The study of the high frequency vibrations revealed these basic characteristics.

(*1*) *Duration:* The groups of high frequency vibrations were usually *shorter* than those recorded in the medium-low frequency bands (Figs. 2, 3, 4B).

(*2*) *Timing:* The high frequency vibrations often appeared at the beginning of the equivalent vibrations in the medium-low bands. Sometimes they coincided with the peaks of such vibrations. As they were shorter, their end occurred *earlier* than that of lower frequency vibrations (Figs. 2, 3, 4B).

(*3*) *Amplitude:* According to a law of physics, the amplitude of all sound vibrations decreases in passing from the lower to the higher frequency bands. In order to register a tracing which can be correctly interpreted, greater electronic amplification is necessary for the higher frequencies (50 to 70 decibels for the No. 3000 galvanometer, 40 to 50 decibels for the No. 1100 galvanometer). In certain cases, this greater electronic amplification was followed by an increase in amplitude of certain components of the heart sounds and murmurs. This was called *relative increase.* In other cases, on the contrary, the amplitude of these vibrations decreased in spite of the greater amplification. The term *relative decrease* was used for this.

(*4*) *Clarity:* Several clinical phenomena were revealed better by the high frequency bands. These included the physiologic or pathologic splitting of the first sound; the physiologic or pathologic splitting of the second sound; the opening snap and certain murmurs.

Tracings recorded in the high frequency bands often revealed more clearly the *shape* of a murmur (presystolic in crescendo, systolic diamond-shaped or crescendo, diastolic decrescendo, etc.). Of the various valvular defects, the murmurs of mitral insufficiency and aortic insufficiency were particularly well revealed by the high frequency bands. In cases of aortic stenosis, the high frequency vibrations were well represented in the murmur and were centrally located (near the peak), so that the murmur appeared shorter than in the medium-low bands.

HEART SOUNDS

In normal cases, the first sound was either relatively decreased (three out of five cases) or increased (two out of five) in amplitude; it was always shorter in duration, and it almost always (four out of five cases) occurred early.* The second sound always had a relative increase in the 500-1000 band while a relative decrease occurred in two out of five cases above 1000 c.p.s. This sound was often shorter and occurred early (three out of five cases).*

In cases with questionable splitting of the first or second sound, the high frequency bands always revealed a definite splitting of these sounds. In some of the cases, splitting was only present in the high frequency bands. Minor murmurs of these subjects always disappeared in the high frequency bands.

A relative increase of the first and second sounds in the high frequency range was usually found in cases of mitral stenosis (Figs. 4, 5), mitral insufficiency and pericarditis. Relative increase of the second sound was commonly found in aortic insufficiency (Fig. 6), hypertensive heart disease and cor pulmonale.

A relative decrease (or disappearance) of the first and second sounds in the high frequency range was noted in cases of aortic stenosis (Fig. 7) and in two-thirds of the cases with myocarditis or congenital heart disease.

The high frequency vibrations of both the first and second sound often occurred *earlier*

* Early occurrence means that the high frequency vibrations took place at the time of the early vibrations of the "stethoscopic" tracing. They started with the first large vibrations of the heart sounds in the latter tracing and terminated within the first one-half or two-thirds of these sounds.

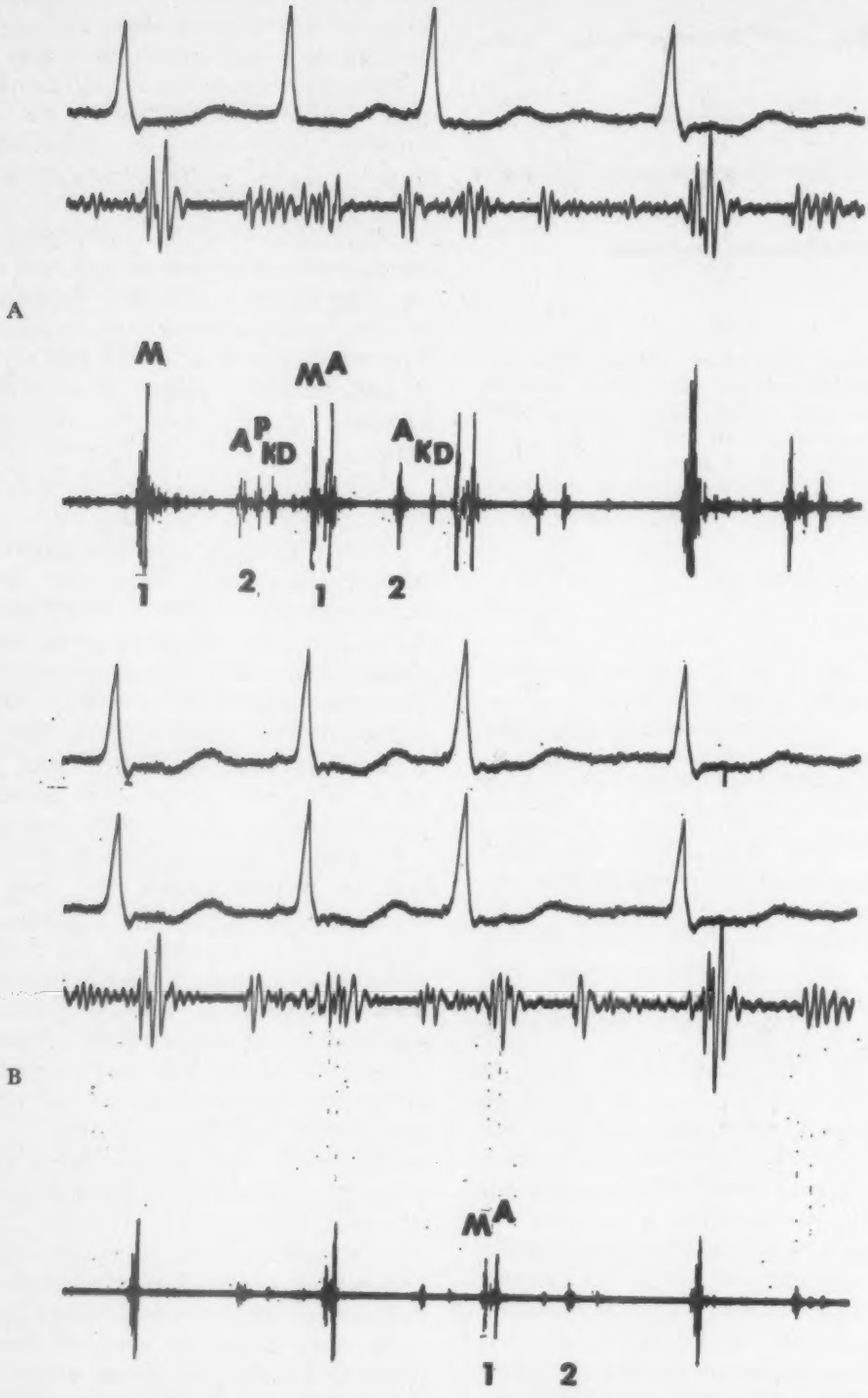

FIG. 4. Mitral stenosis in a sixty five year old woman with atrial fibrillation. Variable duration of diastoles and systoles. *From above:* electrocardiogram, "stethoscopic" tracing and filtered tracing. A, recorded in the band 240-480. B, band 500-750. In both filtered tracings, one can observe a variable splitting of both the first and the second sounds, and also an opening snap (KD). In (A) a small systolic murmur and a few diastolic vibrations are visible. In (B) the second sound is extremely reduced in amplitude. Certain cycles simulate a triplication of the second sound (A, P, KD).

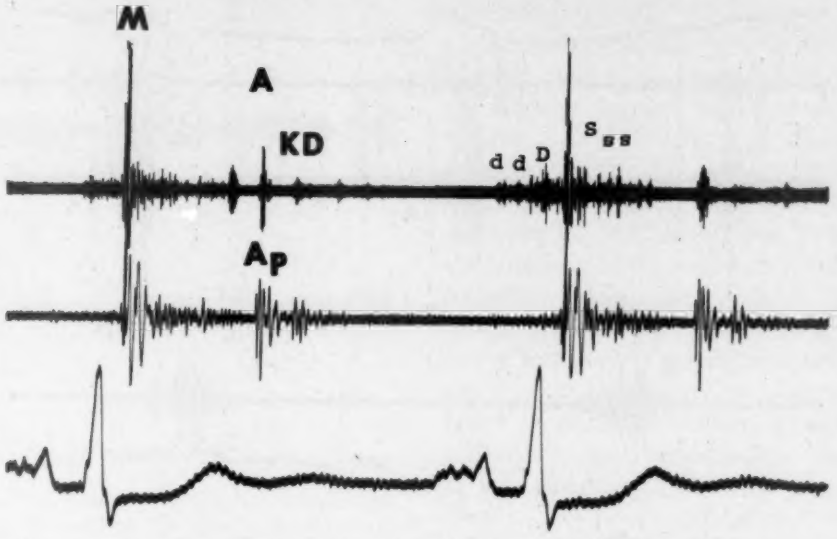

FIG. 5. Mitral stenosis (severe) and insufficiency (mild) in a thirty-five year old woman. *From above:* filtered tracing at apex (240-480 cycles per second), stethoscopic tracing within apex, electrocardiogram. Presystolic (d) and systolic (S) murmurs, opening snap (KD), minor diastolic vibrations.

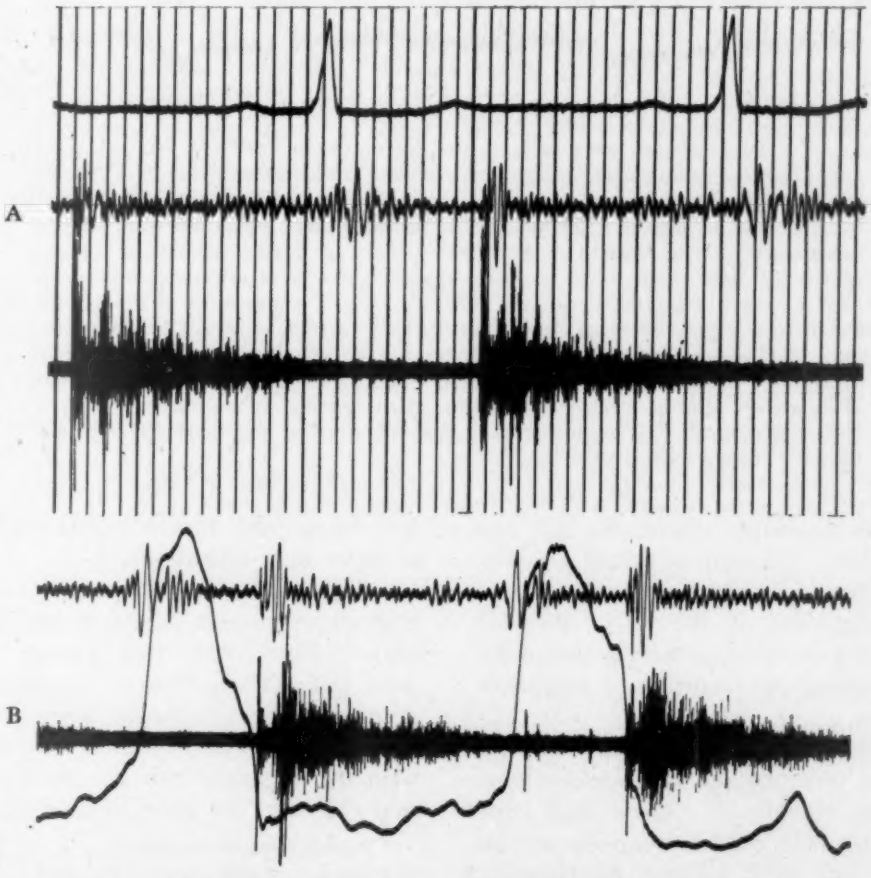

FIG. 6. Aortic insufficiency in a twenty-one year old woman. Diastolic murmur (crescendo-decrescendo type) revealed by the highest frequency ranges. A, *from above:* electrocardiogram, "stethoscopic" tracing, filtered tracing (750–1000). B, *from above:* "stethoscopic" tracing, pulse of suprasternal notch, filtered tracing (1000-2000).

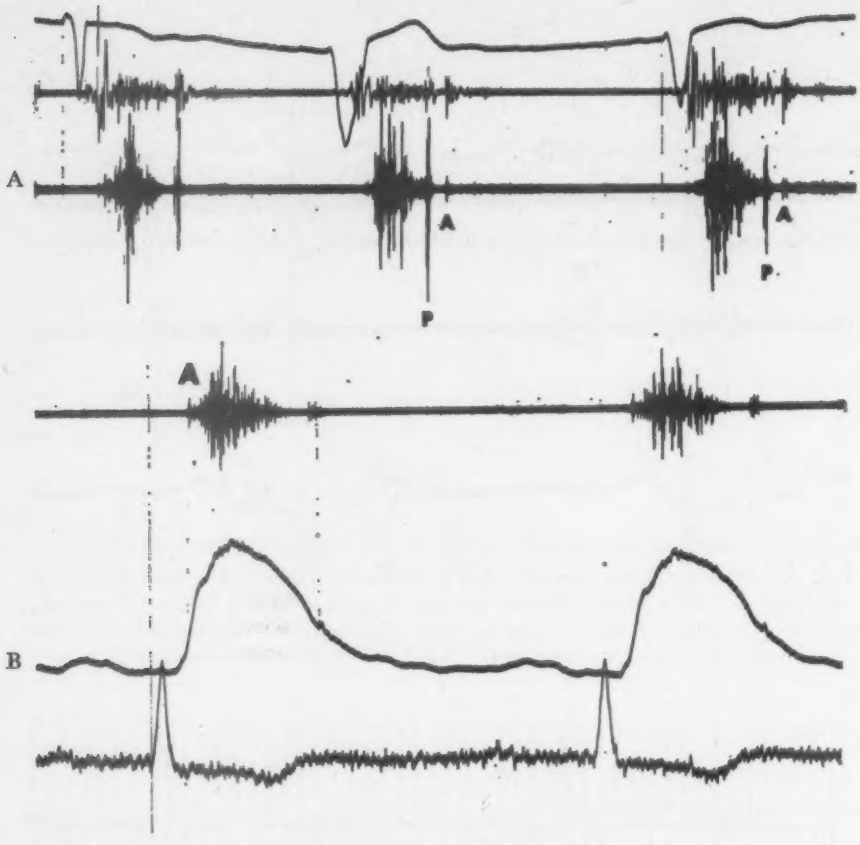

FIG. 7. Two cases of aortic stenosis. A, seventy-one year old woman with atrial fibrillation and ventricular ectopic beats. Tracings recorded over second left interspace (pulmonic area). *From above:* electrocardiogram, "stethoscopic" tracing, filtered tracing (500-750). The murmur starts suddenly with a large vibration ("ejection sound"). Prior to this, there are smaller vibrations belonging to the first sound. The murmur is made of several groups of vibrations and is clearly diamond-shaped. There is a large P component of the second sound and a delayed small A component (paradoxical splitting) in the second and third cycle (ectopic beats). There are small vibrations of a diastolic murmur. B, seventy year old woman. Tracings recorded over aortic area. *From above:* filtered tracing (500-1000), pulse tracing at suprasternal notch, electrocardiogram. Diamond-shaped murmur starting with a small "ejection sound." Small second sound.

than the corresponding vibrations in the medium-low range. In cases of mitral stenosis, they were delayed in comparison with normal subjects (prolongation of the Q-1 interval) but still took place in the very early phase of the corresponding vibrations recorded in the lower frequency range.

Splitting of the First Sound: The first sound, if recorded in the medium-low frequency range, often shows *four* vibrations. These had been found to coincide with the four valvular events of the heart[11] and were labeled M (mitral), T (tricuspid), P (pulmonic) and A (aortic) in this order.* When medium-high frequency bands (240-480) were used,[11] two groups of vibrations were often clearly revealed, usually coinciding with the first (M) and the last (A) of these four vibrations.

When high frequency bands (500-1000 or higher) were used, a further simplification took place. First, only two groups of vibrations were left. Their time of occurrence and their coincidence with lower frequency vibrations and pulse tracings revealed that they coincided with the events of the left heart, i.e., with the first (M) and the last (A) vibrations of the first

* Recent experimental studies in this laboratory show that the initial vibrations of the first heart sound occur during the ascent of pressure in the left and right ventricles, 22 to 23 milliseconds after closure. Therefore, M represents a dynamic event indirectly associated with mitral closure but not simultaneously with it. The same is true for T in regard to tricuspid closure.

FIG. 8. Friction rubs in a nine year old boy with rheumatic pericarditis. *From above:* filtered tracing (500-1000), "stethoscopic" tracing, electrocardiogram. There are three groups of vibrations (F, F, F): in presystole, midsystole, and early diastole. The presystolic rub is sharply separated from the first sound. The systolic rub is also well separated from the heart sounds. The second sound is split.

sound (Figs. 2, 3, 4, 8). They were usually simple and short, each often consisting of a single vibration or, occasionally, a group of two to three vibrations, taking place at the beginning of the corresponding vibration recorded in the medium-high range. In eleven out of twelve cases, the optimum range for observing a split first sound was 500-1000 c.p.s.; in one it was 1000-2000. Often one of the two vibrations became relatively larger in the highest bands; this was more common for the mitral (M) (six out of twelve) (Fig. 2) than for the aortic (A) vibration (four out of twelve) (Fig. 3). In two cases, splitting disappeared at the highest frequencies simply because one of the two vibrations (A in one, M in one) disappeared. It is significant that splitting of the first sound was present in five out of ten cases of mitral stenosis. It is interesting to note that splitting of the first sound was noted in normal subjects as well as in cases of mitral stenosis, myocarditis and pericarditis. It was not noted in cases of mitral or aortic insufficiency or aortic stenosis.*

The optimum range for the M component of the first sound was found to be from 120-240 c.p.s. to 240-480, while the maximum range where this component was present was found to be 1000-2000 c.p.s. (Table 1). The optimum range for the A component of the first sound was from 60-120 to 240-480 c.p.s. The maximum

* Usually, in cases of aortic stenosis, there was first "the first sound," then "the ejection sound." These two groups of vibrations have been considered by us as corresponding to the M and A groups of vibrations of normal subjects, although with *a delay of A*, explained by the higher level of left ventricular pressure necessary for opening the aortic valve.

TABLE 1

Optimum and Maximum Frequency Bands for the Various Cardiac Vibrations (Sounds)

Sound	Optimum Range (c.p.s.)	Maximum Range (c.p.s.)
1st sound		
1 M*	120-240 to 240-480	1000-2000
1 A†	60-120 to 240-480	1000-2000
2nd sound		
2 A‡	240-480	1000-2000
2 P§	120-240 to 240-480 (normal) 750-2000 (pathologic)	1000-2000
3rd, 4th, or summation sound	30-60 (normal) to 60-120 (pathologic)	60-120 (normal) 240-480 (pathologic) (exceptionally 500-1000)
"Ejection sound"	240-480	500-1000
Opening snap	240-480	750-1000 (occasionally 2000)

* Mitral component of 1st sound = 1st large vibration.
† Aortic component of 1st sound = 4th large vibration.
‡ Aortic component of 2nd sound = 1st large vibration.
§ Pulmonic component of 2nd sound = 2nd large vibration.

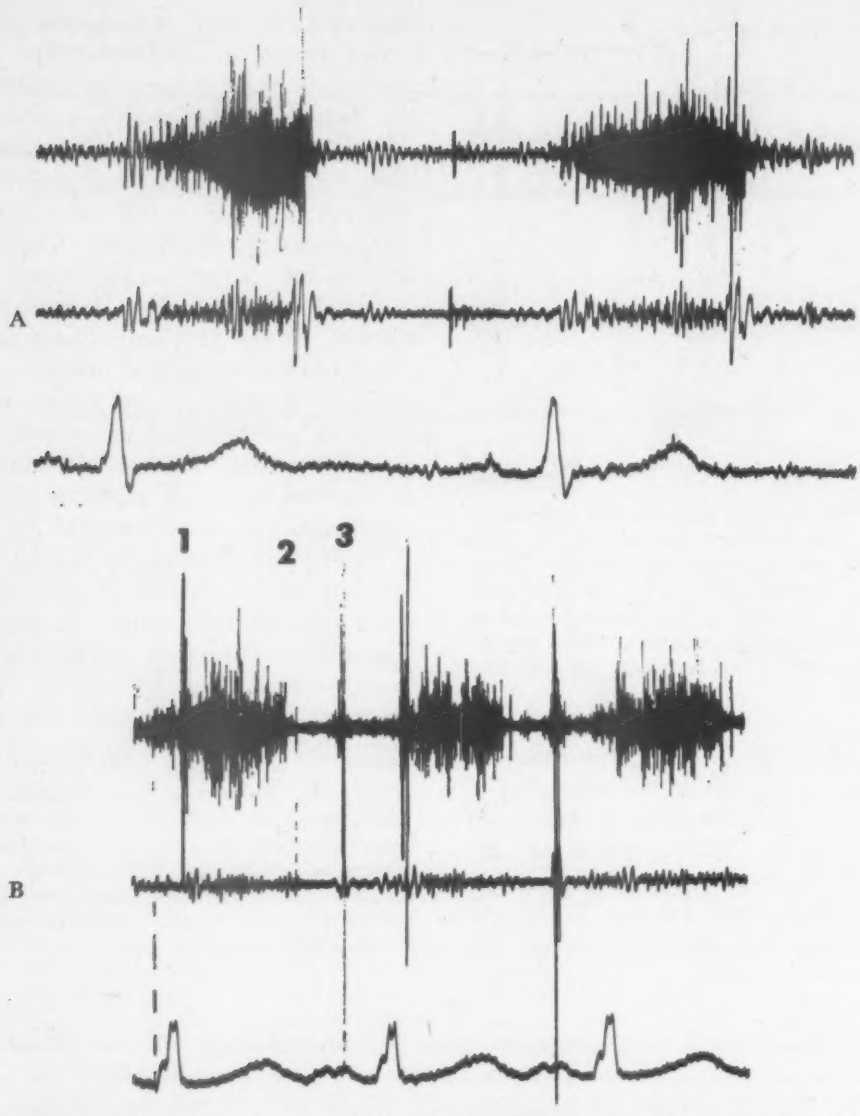

FIG. 9. Two cases of predominant mitral insufficiency. A, forty-one year old woman with organic mitral lesion. B, sixteen year old girl with myocarditis (relative mitral insufficiency and stenosis demonstrated by left heart catheterization). *From above:* filtered tracing (500-1000), "stethoscopic" tracing, electrocardiogram. Case (A) has a crescendo systolic murmur and a large second sound; minor vibrations in diastole. Case (B) has an all systolic murmur, a large first sound, a large third sound (or possibly a summation sound), and a small diastolic-presystolic murmur starting with the third sound.

range was again 1000-2000 c.p.s. (Table 1).

Splitting of the Second Sound: The second sound, if recorded in the medium-low frequency range, may show two vibrations. These were found to be due respectively to closure of the aortic (A) and pulmonic (P) valves.[11] The medium-high frequency bands show this splitting even more clearly, as it had been pointed out by Leatham.[1]

When high frequency bands (500-1000 or higher) were used, splitting became extremely clear (Fig. 3). This occurred in three out of five normal subjects, in five out of thirteen cases of mitral stenosis or insufficiency, in four out of eight cases of myocarditis or pericarditis, and in two out of four undiagnosed cases. The optimum range for recording this splitting was in the 500-1000 c.p.s. octave. The maximum range where splitting was still present was usually above 1000, occasionally up to 2000 c.p.s.* In general, the first (A) vibration was

* These extremely high frequency vibrations were recorded only in young persons with a lean body and a flat chest.

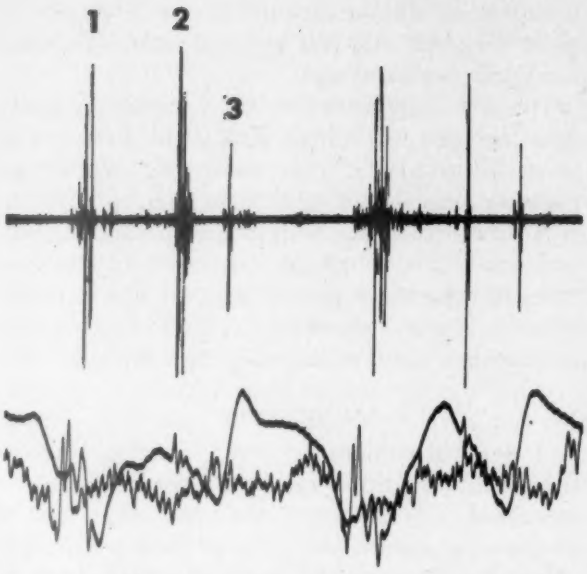

FIG. 10. Triple rhythm due to early diastolic additional sound in a fourteen year old boy with myocarditis (demonstrated by postmortem examination). *From above:* filtered tracing (200-400), apex beat, electrocardiogram (muscular currents are present). The tracings in the higher ranges failed to reveal the triple rhythm.

larger than the second (P). However, the P vibration was the first and was larger in one case of aortic stenosis and insufficiency (weaker A, paradoxical splitting) (Fig. 7A); it was the second and was larger in one case of chronic cor pulmonale, one case of mitral insufficiency, one case of mitral stenosis and one case of myocarditis (pulmonary hypertension).

The optimum range for the A component of the second sound was found to be in the 240-480 c.p.s. range. The maximum range for this component was 1000-2000 c.p.s. The optimum range for the P component of the second sound was found to be 120-240 or 240-480 c.p.s. for subjects with normal pulmonic pressure and up to 750-1500 c.p.s. in cases with severe pulmonary hypertension. The maximum range for this component was found to be 1000-2000 c.p.s. (Table 1).

Ejection Sound: The "ejection sound" was studied in five cases (three cases of aortic stenosis, one case of aortic insufficiency, and one case of chronic cor pulmonale). In all cases, the high frequency tracings revealed a smaller amplitude of this sound in comparison with the same vibration recorded in a lower frequency range (Table 1). Maximal range where this sound was recorded was 500-1000 c.p.s., but its vibrations were relatively smaller than in lower frequency bands. Thus, the ejection sound (or ejection component of the first sound) became less clearly visible when recording a high frequency tracing. The interval between the mitral (M) component of the first sound and the "ejection sound" in cases of aortic valve disease was found of the order of fifty to sixty milliseconds.*

The "ejection sound" was recorded best in the 240-480 c.p.s. range but could usually still be recorded as a small vibration up to 1000 c.p.s. In cases of aortic stenosis, the M component often disappeared in the 500-1000 range, so that the "ejection sound" became the first large visible vibration (Fig. 7B).

Third and Fourth Sounds: The third and fourth sounds had an optimum range in the 30-60 c.p.s. frequency band and could be recorded up to the 60-120 band. However, pathologic third or fourth sounds, or a summation sound (triple rhythms), were recorded best in the 60-120 c.p.s. range, and could still be recorded in the 240-480 range (Table 1; Figs. 9B, 10).

Opening Snap of Mitral Valve: This sound had an optimum range in the 240-480 c.p.s. band. It was still recorded, though with a small amplitude, in the 750-1000 c.p.s. range, and occasionally up to 2000 c.p.s. The band 500-1000 c.p.s., however, often gave a much clearer tracing than lower bands, due to the disappearance of other smaller vibrations which were present in the latter between the second sound and the opening snap (Fig. 4A).

Differential Diagnosis Between Split Second Sound and Opening Snap of the Mitral Valve: This problem often arises in the reading of phonocardiograms. Records taken in the high frequency range theoretically do not help in the differentiation between the P component of the second sound and the opening snap because both are found in the same frequency range. However, this only applies to the P component of the average cases, where the time interval between the two components of the second sound is narrower than that between A component and opening snap. Patients with pulmonary hypertension having a wider splitting of the second sound (0.06 to 0.08 second) frequently have a P component of greater magnitude and higher frequency (see Table 1). In such cases, the frequency alone is sufficient for excluding an opening snap. Cases with

* This is longer than the *normal* M-A interval (thirty to forty-five milliseconds) found in our high frequency tracings, and can be explained by a slightly delayed opening of the aortic valve.

wide splitting of the second sound due to increased flow or bundle branch block may still have a P component in the same frequency range as the opening snap. Therefore, no aid to diagnosis would be obtained in such cases by the study of the high frequency vibrations.

MURMURS

Three possibilities were noted in recording murmurs in the high frequency range:

I. They disappeared and could not be recorded even with maximal amplification.

II. They were still present and were basically unchanged.

III. They became more clearly visible; then, they fell into one of the three following categories:

A. Certain murmurs having both low and high frequency components had *more high frequency components in a typical phase of the cardiac cycle;* in such cases, the high frequency tracing showed the typical "shape" of the murmur more clearly.

B. Other murmurs having both low and high frequency components had *relatively larger high frequency components;* in such cases, the high frequency tracing showed that the murmur had a relatively greater amplitude although its "shape" was similar to that recorded in a lower band.

C. Other murmurs had a definite predominance of high frequency vibrations or had *only* high frequency vibrations; then, *only the high frequency tracing revealed the murmur.*

In *mitral stenosis,* the high frequency presystolic murmur had a more typical "shape" in two cases and a greater amplitude in two other cases. On the whole, the best bands for recording the presystolic murmurs were either 120–240 or 240–480 c.p.s. (Fig. 5). On the other hand, the diastolic murmur disappeared in five out of ten cases, and was still present in one.

In *aortic stenosis,* the high frequency murmur was similar to that recorded in the lower bands in five out of ten cases; it revealed its diamond "shape" better in four out of ten (Fig. 7A); and had a greater amplitude in one out of ten.

In *mitral insufficiency,* the high frequency murmur disappeared in one out of eight and was unchanged in another. It revealed a more typical "shape" in three out of eight (Fig. 9A); it showed a greater amplitude in three out of eight (Fig. 9B); *it only appeared in high frequency tracings in two out of eight.*

In *aortic insufficiency,* the high frequency murmur revealed its typical "shape" in three out of seven (Fig. 6); *it was present only in the high frequency range in four out of seven cases.*

A similar improvement in the graphic characteristics of the murmur was found in the two cases of *hypertensive heart disease,* in the six cases of *pericarditis and myocarditis* (Fig. 8), and in one out of three cases of *congenital heart disease.*

COMMENTS

A new instrument or device is of no importance in itself, and is valuable only insofar as its use allows us to increase our knowledge, first of physiologic events and then of their pathologic changes. The new phonocardiograph used in our study has, among other qualities, that of being able to faithfully record vibrations in the high frequency range, i.e., above 300 c.p.s. Special tests excluded the possibility that the recorded vibrations were artefacts created in the system by the effect of the low or medium frequency vibrations.

The study of these high frequency vibrations has revealed interesting data. The heart sounds and murmurs include not only low and medium-low frequency vibrations but also medium-high and high frequency harmonics and overtones. When one successively records medium frequency, and then high frequency tracings, a gradual simplification of the pattern takes place. This is due to the fact that the high frequency filtration renders the vibrations visually *shorter and simpler.* They appear *at the beginning* of the equivalent medium frequency vibrations and they may have *a relative increase in amplitude.**

Both the physiologic and the pathologic splitting of the first and second heart sounds become more evident by recording high frequency vibrations and are occasionally revealed only by the latter. This was true both in normal subjects and in pathologic cases. No splitting of the first sound, however, was noted in cases of aortic valve disease or in mitral insufficiency. This statement, however, does not apply to the "ejection sound" which was noted in cases with aortic valve disease. No splitting of the second sound was revealed in cases of aortic insufficiency.

* See page 53.

Previous studies[11] had identified the four valvular components of the first sound when this was recorded in the medium-low frequency range. The present observations reveal that the first (mitral closure) and the fourth (aortic opening) component are those most often accompanied by high frequency vibrations. As the rate of change of velocity and the energy imparted to the blood in the left side of the heart and aorta are many times greater than those of the right heart and pulmonary artery, it seems logical that vibrations of a higher frequency and greater magnitude in the higher frequency range originate predominantly in the left side of the heart.

One-half of the cases of mitral stenosis had evident splitting of the first sound. The interval between the two components was usually narrower than normal (average twenty milliseconds instead of thirty to forty-five milliseconds in normal subjects). This can be explained by the fact that in such cases there is a delayed closure of the mitral valve due to the higher left atrial pressure; this causes a delay of the first large vibration of the first sound. On the other hand, as the aortic pressure of these cases is either normal or low, the fourth vibration of the first sound would not be delayed. As a result, the duration of the tension period of the left ventricle (thirty to forty-five milliseconds according to our phonocardiographic studies; about sixty milliseconds according to pressure studies of Braunwald et al.[12]) would become substantially shorter. This confirms that the second large group of vibrations of the first sound in tracings recorded in the medium-high and high frequency ranges is connected with the acceleration of blood taking place at the time of aortic opening and not with the closure of the tricuspid valve.*

Both the "ejection sound" and the opening snap of the mitral valve can be recorded in the high frequency range but are often reduced in amplitude. This is particularly true of the opening snap which, however, is often better visible because of a clearer baseline between the P (pulmonic) component of the second sound and this snap. Both the "ejection sound" and the opening snap are either small or disappear in the 1000-2000 c.p.s. band. This might be explained by the slow acceleration which takes place through a stenotic orifice and which is responsible for these sounds.

The third and fourth sounds are never recorded in the higher frequency range. The mechanism of their production and the relatively slow acceleration occurring at the time of diastolic filling, whether early diastolic or presystolic, explain this.

Splitting of the second sound is usually well revealed by high frequency tracings due to the gradual disappearance of vibrations of a lower pitch, which might be present between the aortic and pulmonic components when the tracing is recorded in the lower bands. However, the higher bands usually show that the aortic component has larger high frequency vibrations than the pulmonic.

In cases of pulmonary hypertension, when the pulmonic component is larger in the medium and medium-high ranges, the pulmonic component is even larger in the highest range. Greater deceleration in the aorta and left ventricle in the majority of subjects, and greater deceleration in the right ventricle and pulmonary artery in cases of pulmonary hypertension are probably responsible for these facts.

Murmurs may become more or less evident in the high range according to their fundamental frequency and the percentage of high frequency components. As expected, the low-pitched diastolic murmur of mitral stenosis disappears. On the other hand, the presystolic murmur of mitral stenosis may become more evident. In a good percentage of cases the murmur of aortic stenosis reveals its typical shape better or becomes larger in the high frequency range. Murmurs of mitral or aortic insufficiency are better recorded in the high frequency range: in some cases, they are recorded only in this range.

In conclusion, while certain murmurs disappear or persist unchanged in the high frequency range, others become more clearly visible, and others may be such as to be recorded only in the high frequency range.

Summary

A systematic study of the high frequency components of the heart sounds and murmurs was made by means of a new standardized and calibrated phonocardiograph provided with a variable band pass filter. The frequency bands 500-1000 c.p.s. and higher were partic-

* According to Braunwald et al.[12] the average interval between mitral and tricuspid closure of normal subjects is thirteen milliseconds. In cases with mitral stenosis, this interval would become near zero (or even be reversed) because there is a delay of mitral closure which is in the range of ten to forty milliseconds.

ularly studied but comparison was also made with the vibrations found in lower bands.

This study was made in forty-seven subjects including five subjects without evidence of heart disease. The study revealed that the groups of high frequency vibrations were normally shorter than the equivalent group of lower bands; they often (but not always) appeared at the beginning of equivalent vibrations; they often presented a relative increase of amplitude.

Several clinical phenomena were better revealed by the study of high frequency bands including the physiologic or pathologic splitting of the first and second sounds, the opening snap, and certain murmurs. The high frequency bands often revealed more clearly the "shape" of a murmur. In some cases, splitting of the heart sounds or the existence of a murmur was revealed only by these bands.

The high frequency bands revealed that in about 25 per cent of the cases the first sound was composed of two simple vibrations (or groups of vibrations). These were identified through their time of occurrence as coinciding with mitral closure and aortic opening. One of the two may disappear in the highest band.

The high frequency bands revealed that in more than one-third of the cases the second sound was composed of two simple vibrations (or groups of vibrations). These were identified as coinciding with aortic closure and pulmonic closure. The latter usually disappeared in the highest band except in cases of pulmonary hypertension.

The optimum and maximum frequency bands in both normal subjects and clinical cases were studied for the first and second sounds, as well as for the third and fourth. A similar study was made in regard to the "ejection sound" and the opening snap of the mitral valve.

Murmurs recorded in the high frequency range either disappeared, were still present, or became more clearly visible. The murmurs of mitral and aortic insufficiency were usually in the last group and were sometimes recorded only in the high frequency range. Detailed observations were made in the various valvular defects.

It is concluded that the study of the high frequency vibrations of the phonocardiogram presents great interest both in normal subjects and in clinical cases. In the latter, it may be of diagnostic importance. Problems of cardiovascular physiology and pathology may at times be clarified by this study.

References

1. Leatham, A. Phonocardiography. *Postgrad. Med. J.*, 25: 568, 1949; *Brit. Med. Bull.*, 8: 333, 1952.
2. Mannheimer, E. Calibrated phonocardiography and electrocardiography. *Acta Paediat.*, 28: Suppl. II, 1940.
3. Maass, H. and Weber, A. Herzschallregistrierung mittels differenzierenden Filter: eine Studie zur Herzschallnormung. *Cardiologia*, 21: 6, 1952.
4. Holldack, K. and Wolf, D. Atlas und Kurzgefasstes Lehrbuch der Phonokardiographie. Stuttgart, 1956. Thieme.
5. Butterworth, J. S., Chassin, M. R. and McGrath, R. Cardiac Auscultation, 2nd ed. New York, 1959. Grune & Stratton.
6. Luisdada, A. A. and Zalter, R. Phonocardiography. III. Design of the ideal phonocardiograph. *Am. J. Cardiol.*, 4: 24, 1959.
7. Luisada, A. A. and Zalter, R. A new standardized and calibrated system. *IRE Trans. Med. Electronics*, 7: 15, 1960.
8. Zalter, R., Hodara, H. and Luisada, A. A. Phonocardiography. I. General principles and problems of standardization. *Am J Cardiol.*, 4: 3, 1959.
9. Zalter, R. and Luisada, A. A. Phonocardiography. II. Appraisal and critical analysis of existing systems. *Am. J. Cardiol.*, 4: 16, 1959.
10. Luisada, A. A. The expanding horizon of phonocardiography. *Arch Kreislaufforsch.*, 33:38, 1960.
11. Luisada, A. A., Liu, C. K., Aravanis, C., Testelli, M. R. and Morris, J. On the mechanism of production of the heart sounds. *Am. Heart J.*, 55: 383, 1958.
12. Braunwald, E., Fishman, A. P. and Cournand, A. The relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circulation Res.*, 4: 100, 1956.

High Speed Phonocardiography

An Approach to the Frequency Analysis of the Vibrations Originating in the Heart*

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HIGH SPEED phonocardiography is a new method devised for an objective and detailed analysis of the vibrations which compose the heart sounds and murmurs.

It is well known that the timing of auscultatory phenomena and their time relationship with other physiologic parameters are useful for clinical diagnosis. However, the information supplied by conventional phonocardiography may be limited by the technical characteristics of the instruments employed. The frequency analysis of the vibrations of the heart sounds and murmurs at the standard speed of the film (100 mm. per second or less) is sometimes difficult in conventional phonocardiography.

The frequency characteristics of cardiac murmurs were studied by Cabot and Dodge[1] and by Williams and Dodge,[2] who listened to heart murmurs through electric filters. A similar method of filtering and listening was applied by Butterworth et al.[3]. They found most systolic murmurs between 80 and 120 c.p.s., most mitral diastolic murmurs between 40 and 100 c.p.s. and most aortic and pulmonic diastolic murmurs between 100 and 120 c.p.s.

In 1938 Mannheimer[4] described "calibrated phonocardiography," a useful method for analysis of the cardiac vibrations. Another method of "calibrated phonocardiography" was more recently described by Maass and Weber.[5] In 1956 Luisada and co-workers[6] described the method of "selective phonocardiography." "Spectral phonocardiography" (McKusick[7]) is another development for the study of frequency of the cardiac vibrations. The method, however, is different from those of conventional phonocardiography.

According to Luisada,[8] one can consider either the entire spectrum of vibrations or limit the study to those vibrations which have a definite clinical importance. The latter correspond to the data of clinical auscultation and are recorded by conventional phonocardiography.[9] While the frequency of cardiac vibrations has often been empirically evaluated in conventional phonocardiograms, an exact count requires special methods.

Several authors have stated that heart sounds and murmurs can exceed 500 c.p.s. At the standard film speed of 100 mm. per second, or less, it would be impossible to record and count these vibrations exactly. Conventional phonocardiograms, therefore, are inadequate for this purpose. With high speed phonocardiography, on the other hand, it is possible to analyze the single vibrations of the heart sounds and murmurs, to study their shape and to count them exactly.

TECHNIC

The apparatus for high speed phonocardiography† includes the following parts: (1) A five gun oscilloscope (Galileo No. R17D) with synchronized beams and a Dumont 7YP7 tube. (2) A cinecamera (Galileo No. R153V). (3) A frequency selector with five filters. These are band-pass filters having a slope of −40 decibels per octave. The frequencies selected were 40 to 80, 80 to 160, 160 to 320, 320 to 640 and 640 to 1280.

This apparatus permitted the simultaneous visualization and recording of two phonocardiograms, two electrocardiograms, and the fifty cycles AC, which was used as a time signal. The simultaneous recording of an arterial or venous pulse instead of an electrocardiogram or of a phonocardiogram was also possible. The sweep speed of the electronic guns of the oscilloscope could vary from 2.5 cm. per second to 15 M. per second , so as to permit the perfect record-

† Built by the O. T. E. Company, Florence, Italy.

* From the Institute of Physical Diagnosis of the University of Siena (Italy), directed by Prof. F. Lenzi.

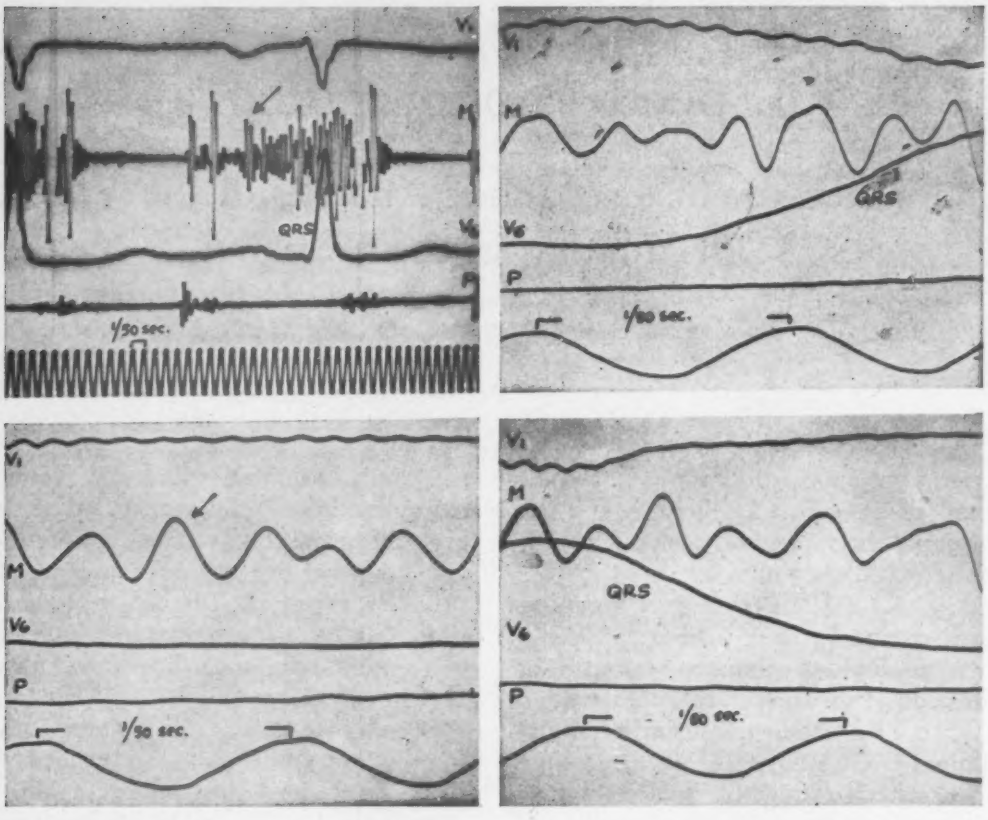

FIG. 1. *Mitral stenosis:* diastolic murmur with presystolic accentuation, loud M_1, mitral opening snap. *Top left:* Simultaneous recording of two electrocardiographic tracings (V_1, V_6), two logarithmic phonocardiographic tracings from mitral (M) and pulmonary (P) areas, and of 50 c.p.s. AC, as time marker. Sweep: 10 cm. per second. *Bottom left, top right* and *bottom right:* High speed analysis of presystolic murmur: logarithmic phonocardiograms from same area at a speed of 2 M. per second.

ing of any type of vibrations including those of high frequency.

The heart sounds were recorded either from two separate areas of the precordium (two phonocardiograms with the same technical characteristics were recorded) or from the same area (two phonocardiograms with different technical characteristics were recorded.) Crystal microphones were used. One amplifier had a flat response from 40 to 8000 c.p.s. while another had a logarithmic response (−14 decibels at 60 c.p.s., −8 decibels at 100 c.p.s., −4 decibels at 400 c.p.s., −2 decibels at 600 c.p.s., 0 decibels at 1000 c.p.s.). This system provided a harmonic analysis of heart sounds and murmurs and an accurate study of the frequencies of the single bands examined.[10–15]

RESULTS

MAIN VIBRATIONS OF HEART SOUNDS AND MURMURS

Using the method described, the basic vibrations of the cardiac sounds and murmurs were recorded.

Heart murmurs were seen to be composed of a series of vibrations rather irregular in shape and frequency with the exception of musical murmurs, which were made of equal vibrations like a pure sine wave. A study of the basic frequencies[10–15] revealed that the fundamental frequencies of the greatest number of murmurs (including the murmurs of mitral stenosis, ventricular septal defect, aortic or pulmonic stenosis and aortic or pulmonic dilatation) were less than 150 c.p.s. while murmurs of aortic insufficiency were usually less than 250, and only a few musical murmurs showed frequencies of 300 to 350 c.p.s.[11]

Mitral Stenosis: Figure 1 deals with a case of mitral stenosis. The standard phonocardiogram records a harsh diastolic murmur which begins after the opening snap of the mitral valve; the first sound is very loud. The high speed phonocardiograms clearly reveal the vibrations of the same murmur with a frequency of 150 c.p.s.

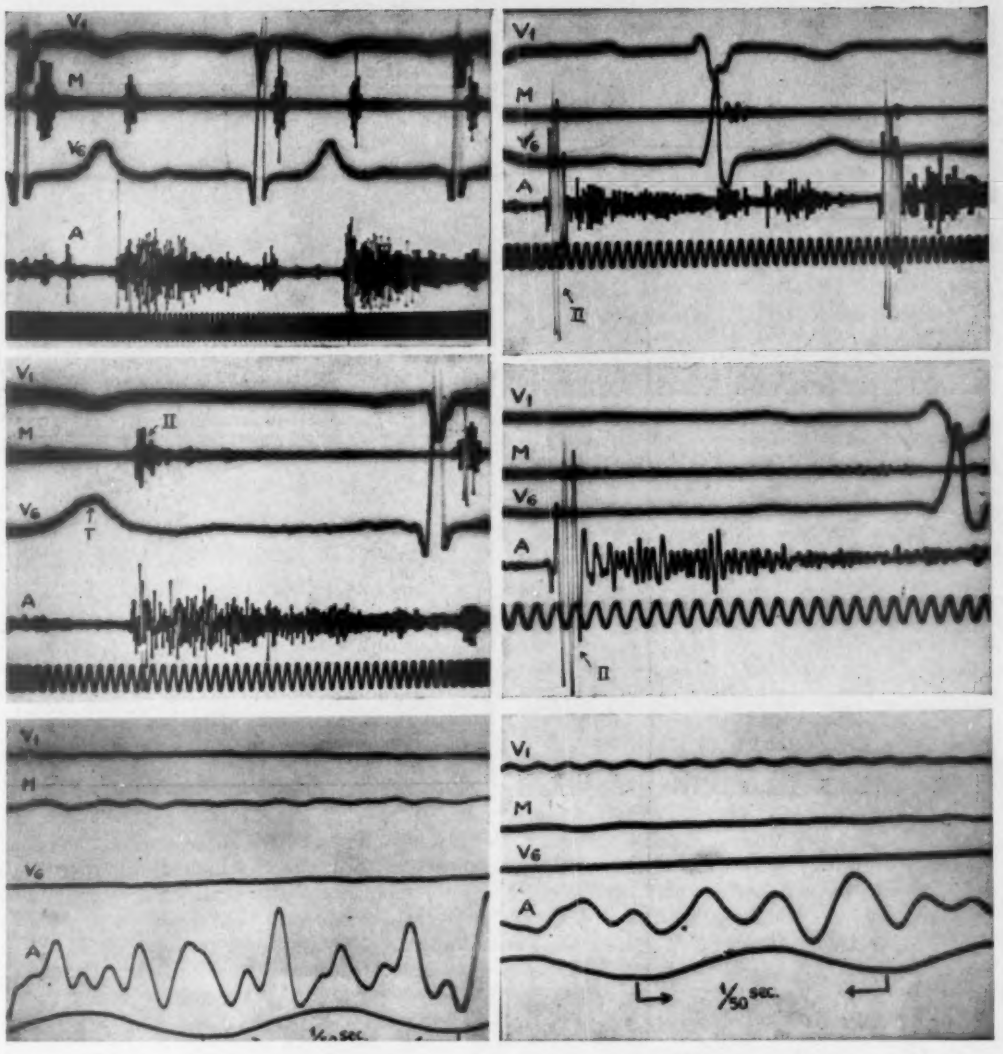

FIG. 2. *Aortic incompetence* (two cases). A, decrescendo aortic diastolic murmur. *Top:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiograms from mitral (M) and aortic (A) areas, and of a 50 c.p.s. AC. Sweep: 5 cm. per second. *Middle:* same recording at 10 cm. per second. *Bottom:* high speed (2.5 M. per second) analysis of diastolic murmur. B, descrescendo aortic diastolic murmur. Loud A_2, faint aortic systolic murmur. *Top:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiograms from mitral (M) and aortic (A) areas and of a 50 c.p.s. AC. Sweep: 10 cm. per second. *Middle:* same recording at 20 cm. per second. *Bottom:* high speed (2.5 M. per second) analysis of diastolic mrmur. Both murmurs were blowiug in quality; the murmurs displayed on the right had a rather low periodicity.

Aortic Insufficiency: The murmurs of two cases of aortic insufficiency are presented in Figure 2. The diastolic murmur in decrescendo recorded over the aortic area is evident in the standard and medium speed phonocardiogram. The case in Figure 2B has a loud second sound. The main vibrations of these diastolic murmurs are quite different in shape and frequency, being 300 c.p.s. in the case on the left and 150 c.p.s. in that on the right. Both murmurs had a typical decrescendo character on auscultation.

Pulmonic Stenosis: Figure 3 deals with a case of pulmonic stenosis. A harsh and loud diamond-shaped systolic murmur was recorded in the second left interspace (see the standard and medium speed phonocardiograms on the left). The main vibrations of this systolic murmur recorded in a high speed phonocardiogram have a rather low frequency (150 c.p.s.).

Tetralogy: Figure 4 shows a phonocardiogram in a case of tetralogy of Fallot following a Blalock operation. The tracing shows a sys-

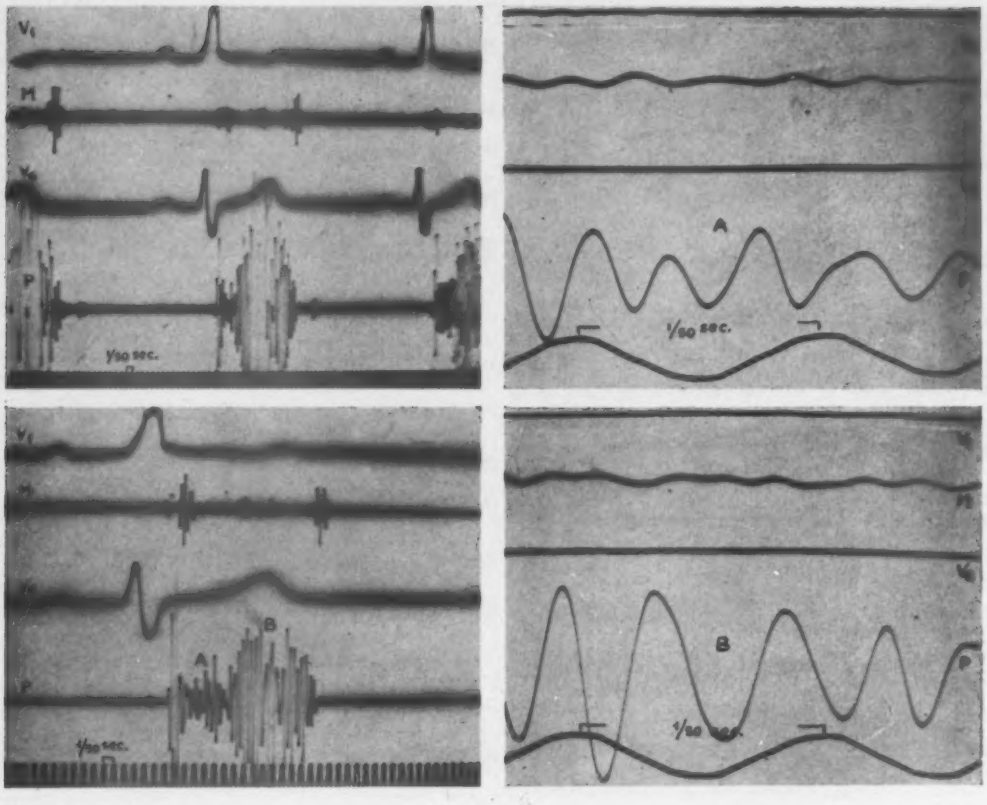

FIG. 3. *Pulmonary stenosis:* Harsh, diamond shaped, systolic murmur in pulmonary area. *Top left:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiograms from mitral (M) and pulmonary (P) areas, and of a 50 c.p.s. AC. Sweep: 5 cm. per second. *Bottom left:* same registration at 10 cm. per second. *Top right:* high speed (2.9 M. per second) analysis of pulmonary systolic murmur (protosystolic phase A). *Bottom right:* high speed (2.9 M. per second) analysis of pulmonary systolic murmur (mesosystolic phase B).

tolic murmur in the mitral area and a continuous murmur in the second left interspace. The irregular shape of the main vibrations and their low frequency (150 to 200 c.p.s. for the systolic murmur, 200 c.p.s. for the diastolic) are revealed.

Musical Murmurs: Figure 5 is the record of a "sea gull murmur" in a case of aortic insufficiency. The vibrations of this musical murmur appear regular in the high speed phonocardiograms (B, C). They are regularly sinusoidal and identical to each other; their frequency is high (300 c.p.s.).

The musical murmurs are actually represented by pure sine waves; their frequency is high as compared to the nonmusical murmurs but not as high as the most "high-pitched" heart sounds.

HARMONIC ANALYSIS OF HEART SOUNDS AND MURMURS

As our apparatus for high speed phonocardiography is provided with a frequency selector which permits simultaneous recording of the same sound (or murmur) in different bands of frequency, a harmonic analysis was made possible, thus permitting differentiation of the phenomenon of diaphonesis from the actual harmonics.

It is well known that vibrations, especially if extremely amplified, may appear, not only on their own frequency bands, but also on contiguous bands, in spite of filters having a slope of −40 decibels per octave. This was experimentally checked by means of a signal generator.

With the harmonic analysis at the standard sweep speed, often tall vibrations in the 80 to 160 c.p.s. band, and smaller vibrations in the upper frequency bands (160 to 320 c.p.s. and 320 to 640 c.p.s.), were observed. Vibrations of high frequency exist sometimes but not always. With high speed phonocardiography it is possible to establish that the small vibrations recorded in the upper frequency bands are often identical in frequency and shape to the main

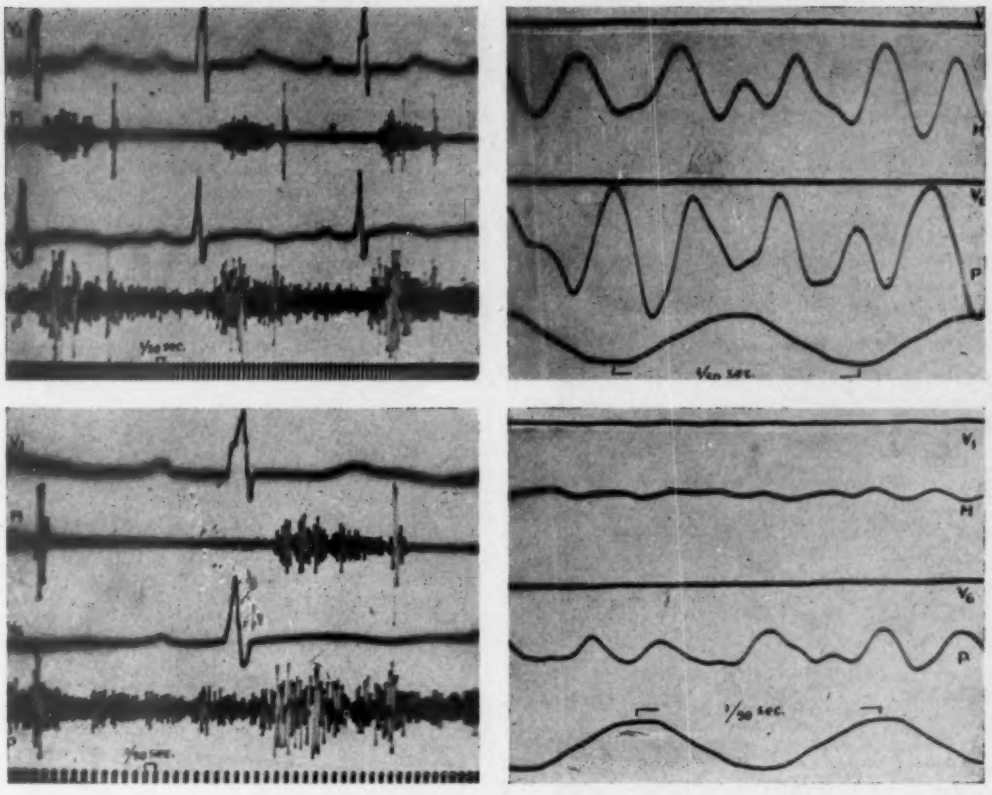

FIG. 4. *Fallot's tetralogy* (after Blalock's operation). Mitral systolic murmur (M), accentuated second sound and continuous murmur at second left intercostal space (subclavicular area). *Top left:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiographic tracings from mitral (M) and left subclavicular (P) areas, and of a 50 c.p.s. AC. Sweep: 5 cm. per second. *Bottom left:* same recording at 10 cm. per second. *Top right:* high speed (2.4 M. per second) analysis of systolic murmur. *Bottom right:* high speed (2.4 M. per second) analysis of diastolic murmur.

vibrations recorded in the 80 to 160 c.p.s. band. Their appearance in the upper frequency bands is then due to diaphonesis.

Diaphonesis: Figure 6 gives an example of diaphonesis. The vibrations recorded in the 160 to 320 c.p.s. band are identical in frequency, and similar in shape, to the vibrations recorded in the 80 to 160 c.p.s. band. On the other hand, when harmonics are really present they are clearly recorded in their own frequency bands.

Harmonics: Figure 7 gives an example of second and third harmonics recorded in a case of mitral stenosis. These vibrations belong to the accentuated first sound. These harmonics are exceptionally widespread. This is more common for heart sounds than for murmurs.

A second harmonic is often visible in our tracings but is always of smaller magnitude than the fundamental vibrations. It appears with greater frequency near the peak of each of the main vibrations. A third harmonic is more seldom recorded.

The upper harmonics are negligible with normal amplification and can be observed only with markedly greater amplification. Their intensity is often not greater than $^1/_{50}$ of that of the main vibrations, and such as to render unlikely their effect on the characterization of the sound to which they belong.

Superimposed Diaphonesis and Harmonics: Vibrations due to diaphonesis and harmonics may be superimposed phenomena; often harmonics correspond to only a few main vibrations, which in other tracings emerge by diaphonesis on the upper frequency bands. This is demonstrated by Figure 8, which presents tracings from a case of syphilitic aortitis. A systolic click is present over both the mitral (M) and aortic (A) areas. A large diamond-shaped systolic murmur with accentuated second sound is present in the aortic record. A high speed phonocardiogram shows that the main vibrations have a frequency of 150 to 200 c.p.s. Another section of the same figure presents the

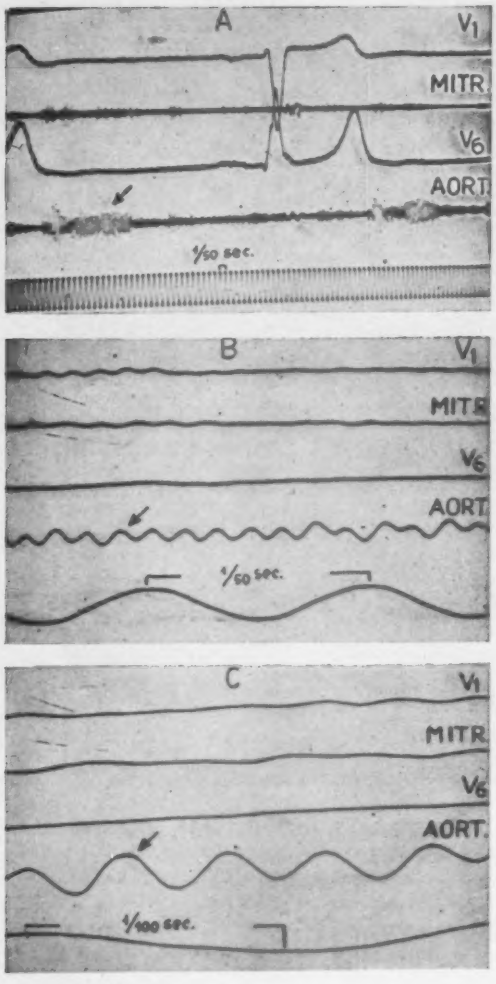

FIG. 5. *Aortic incompetence:* musical (sea gull) aortic diastolic murmur. *Top:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiograms from mitral (Mitr.) and aortic (Aort.) areas, and of a 50 c.p.s. AC. Sweep: 5 cm. per second. *Center:* high speed (2.25 M. per second) analysis of musical aortic diastolic murmur. *Bottom:* high speed (7 M. per second) analysis of musical diastolic murmur. Note the perfect regularity of sine waves of musical murmur.

harmonic analysis of the same murmur at medium and high speed. A second harmonic is clearly recorded in the 160 to 320 frequency band. The first two vibrations pass into the 160 to 320 band by diaphonesis; the others are actually the second harmonics of the fundamental. No harmonic is recorded in the 320 to 640 frequency band, because the amplification is the same in all the frequency bands, and this is inadequate for recording the high frequency vibrations.

Harmonic analysis can be done with greater amplification in the upper frequency bands in

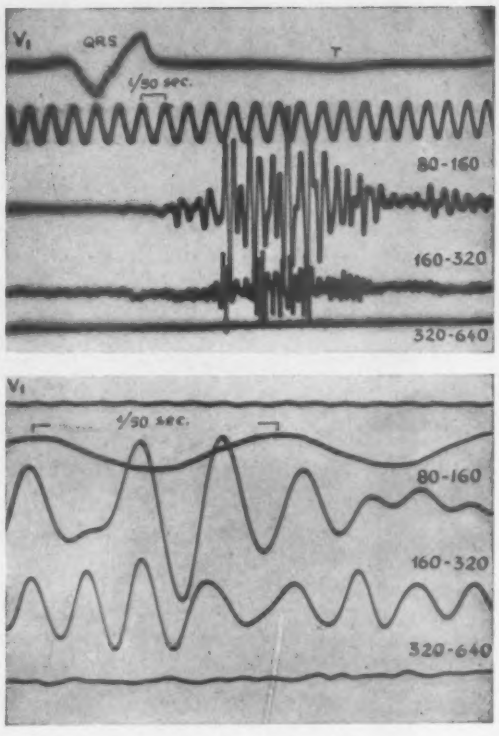

FIG. 6. *Diaphonesis:* diamond-shaped systolic murmur, faint first and second aortic sounds in a case of aortic stenosis. *Top:* simultaneous recording of electrocardiogram (V_1), 50 c.p.s. AC, and of three different frequency bands simultaneously recorded from the same area (80 to 160; 160 to 320; 320 to 640). Sweep: 20 cm. per second. *Bottom:* same registration at 2.2 M. per second. The principle vibrations are evenly inscribed in frequency bands 80 to 160 and 160 to 320.

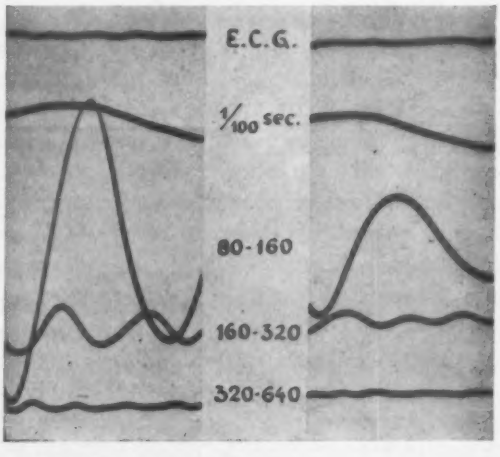

FIG. 7. *Second and third harmonics:* harmonic analysis of an accentuated first sound of mitral stenosis with high speed phonocardiography. *Left:* second harmonic is clearly recorded on 160 to 320 c.p.s. frequency band. *Right:* third harmonic is clearly recorded on 160 to 320 c.p.s. frequency band. Sweep: 2.2 M. per second.

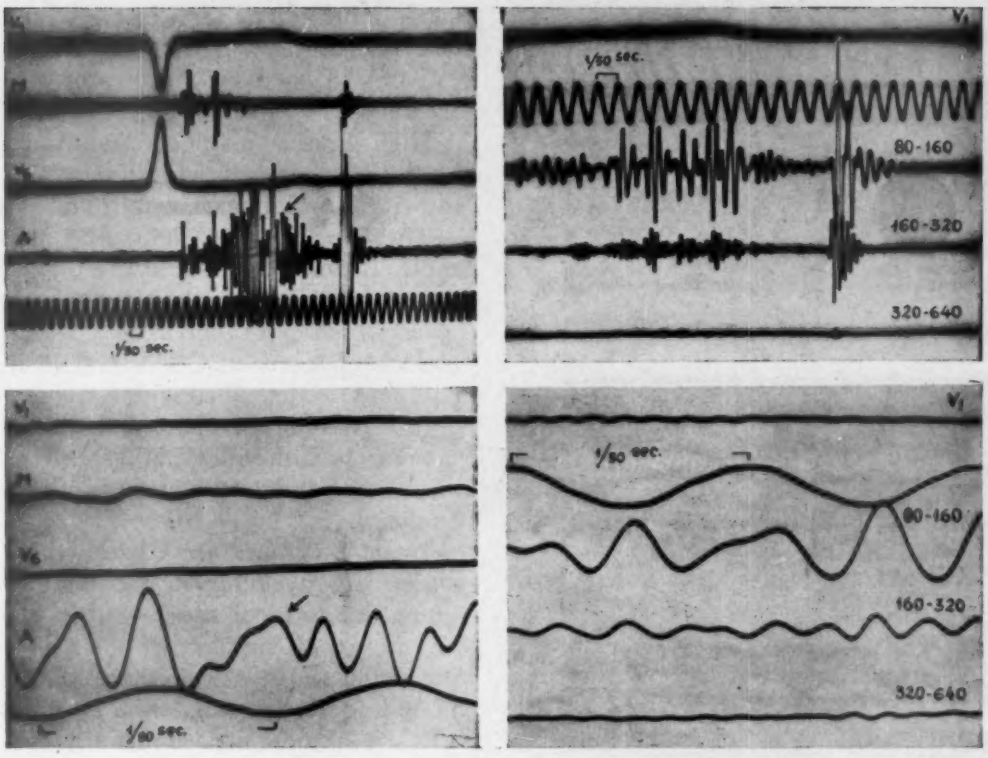

FIG. 8. *Harmonic analysis of aortic systolic murmur* (luetic aortitis): diamond-shaped aortic systolic murmur, accentuated A_2, protosystolic click. *Top left:* simultaneous recording of two electrocardiograms (V_1, V_6), two logarithmic phonocardiograms from mitral (M) and aortic (A) areas, and of a 50 c.p.s. AC. Sweep: 10 cm. per second. *Bottom left:* high speed (2.4 M. per second) analysis of systolic murmur. *Top right:* simultaneous recording of electrocardiogram (V_1), 50 c.p.s. AC, and of three different frequency bands simultaneously recorded from same area (80 to 160; 160 to 320; 320 to 640). Sweep: 20 cm. per second (medium speed harmonic analysis). *Bottom right:* high speed (2.4 M. per second) harmonic analysis of systolic murmur. Note the good inscription of second overtone on three last fundamental vibrations.

order to record vibrations which otherwise would not be visible. Harmonic analysis in a case of aortic insufficiency is presented in Figure 9 in order to study the blowing diastolic murmur "in decrescendo." The high speed phonocardiogram at standard amplification shows a good reproduction of the second harmonic (160 to 320 frequency band); the higher harmonics (320 to 640 frequency band) are very small and sparse.

The amplification is five times greater in the 160 to 320 frequency band and ten times greater in the 320 to 640 frequency band. The second harmonic appears in the 160 to 320 frequency band where some fundamental vibrations are also recorded by diaphonesis (third, fourth, fifth). In the 320 to 640 frequency band, harmonics are well recorded: second harmonic of the third (fundamental) vibration, third harmonic of the fourth and fifth, and fourth harmonic of the sixth vibration.

The amplification required reveals that the energy of the upper harmonic vibrations is small (about $^1/_{50}$ of the main vibrations).

Clinical Applications

From a theoretic point of view, high speed phonocardiography has particular interest as it permits recording and description of the fine details of the sound vibrations of the heart sounds and murmurs. The various component parts of these murmurs are distinctly recorded so that it is easy to establish their frequency and form.

A complete study by means of harmonic analysis allows one to recognize with certainty the harmonics corresponding to each basic vibration, a fact which has practical value. In fact, students of phonocardiography always tried to increase their knowledge of the frequency of vibrations of heart sounds and murmurs. High pitched murmurs, for example, are

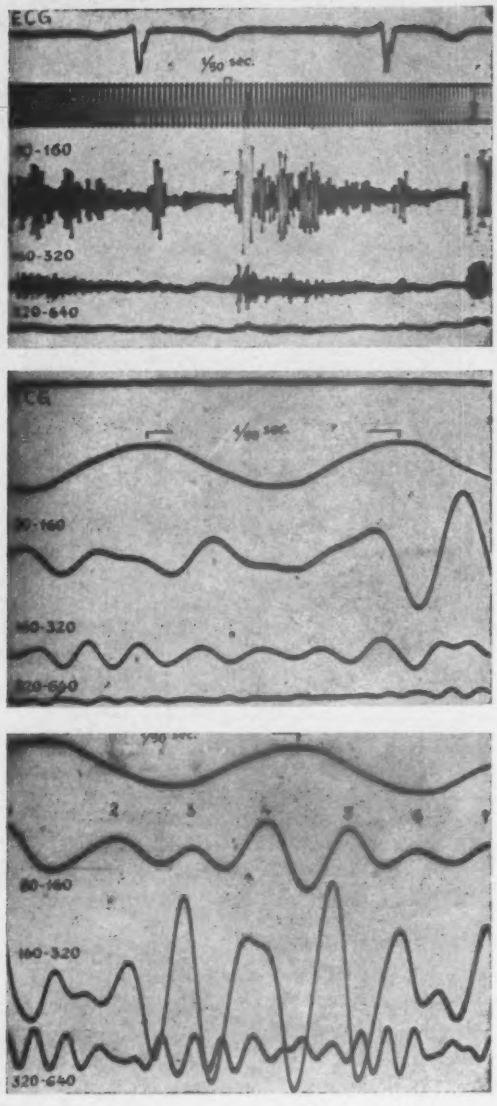

FIG. 9. *Harmonic analysis of diastolic murmur* (aortic incompetence): decrescendo blowing murmur. *Top:* simultaneous recording of electrocardiogram (V_1), 50 c.p.s. AC, and of three different frequency bands simultaneously recorded from same area (80 to 160; 160 to 320; 320 to 640). Sweep: 5 cm. per second. *Center:* high speed (2.4 M. per second) harmonic analysis of diastolic murmur. *Bottom:* high speed (2.4 M. per second) harmonic analysis of diastolic murmur. Amplification of frequency bands 160 to 320 and 320 to 640. Detailed description in text.

characteristic of certain valvular diseases and not of others, so that determination of the basic frequency can have diagnostic value.

High speed phonocardiography supplies more precise information concerning the frequency of a sound than that derived from conventional phonocardiography. For example, the diastolic murmur has a higher average frequency in aortic insufficiency than in mitral stenosis, even when the murmur is "musical."

SUMMARY

High speed phonocardiography makes it possible to analyze objectively and in detail the vibrations of heart sounds and murmurs.

The apparatus for high speed phonocardiography includes a cathode ray oscilloscope with five independent electronic guns and a sweep speed which can range from 2.5 cm. per second to 15 M. per second. This phonocardiographic equipment is provided with a frequency selector of the "pass-band" type which permits the simultaneous recording at high speed of the same sound analyzed at various frequencies (harmonic analysis).

Heart murmurs are composed of vibrations which are irregular in shape and frequency. Only the musical murmurs are composed of vibrations of similar amplitude, following a pure sine wave. With the above technic, the main frequencies were found in the range 100 to 150 c.p.s. for mitral murmurs, in the range 150 to 250 c.p.s. for the murmur of aortic insufficiency. The highest-pitched murmurs are "musical" (300 to 350 c.p.s.).

High speed harmonic analysis clearly records harmonics when they really exist. The second harmonic is often recorded and its intensity is about $^1/_{10}$ of the basic vibrations. The upper harmonics are negligible with average amplification and can only be recorded with greatly increased amplification.

REFERENCES

1. CABOT, R. C. and DODGE, H. F. Frequency characteristics of heart and lung sounds. *J.A.M.A.*, 84: 1794, 1925.
2. WILLIAMS, H. B. and DODGE, H. F. Analysis of heart sounds. *Arch. Int. Med.*, 38: 658, 1926.
3. BUTTERWORTH, J. S., CHASSIN, M. and MCGRATH, R. Cardiac Auscultation. New York, 1955. Grune and Stratton.
4. MANNHEIMER, E. Calibrated phonocardiography. *Acta Paediat. Scandinav.*, suppl. 2: 28, 1940.
5. MAASS, H. and WEBER, A. Herzschall Registrierung mittels differenzierender Filter. *Cardiologia*, 21: 773, 1952.
6. LUISADA, A. A., RICHMOND, L. and ARAVANIS, C. Selective phonocardiography. *Am. Heart J.*, 51: 221, 1956.
7. MCKUSICK, V. A. Spectral phonocardiography: current status as a research, clinical and teaching tool. *Circulation*, *12*: 744, 1955.
8. LUISADA, A. A. Symposium on phonocardiography. Introduction. *Am. J. Cardiol.*, 4: 1, 1959.
9. ZALTER, R., HODARA, H. and LUISADA, A. A. Phonocardiography. 1. General principles and

problems of standardization. *Am. J. Cardiol.*, 4: 3, 1959.

10. Caniggia, A., Bertelli, G. and Lodone, M. Fonocardiografia ad alta velocitá. *Boll. Soc. ital. biol. sper.*, 35: 218, 1959.
11. Caniggia, A. Analisi dei rumori cardiaci musicali con la fonocardiografia ad alta velocitá. *Boll. Soc. ital. cardiol.*, 4: 321, 1959.
12. Caniggia, A., and Bertelli, G. Fonocardiografia ad alta velocitá: analisi delle vibrazioni componenti i toni ed i soffi cardiaci. *Minerva cardioangiol.* 8: 249, 1960.
13. Caniggia, A., Bertelli, G. and Lodone, M. Analisi armonica dei rumori cardiaci condotta con la fonocardiografia ad alta velocitá. *Cuore e circolaz.*, 44: 103, 1960.
14. Caniggia, A., Bertelli, G. and Lodone, M. High speed phonocardiography in aortic insufficiency. *Cardiologia.* In press.
15. Caniggia, A. and Bertelli, G. High speed phonocardiography: analysis of the vibrations of the heart sounds and murmurs. *Panminerva Med.* In press.

Report on Therapy

Colloidally Suspended Phytonadione in Bishydroxycoumarin-Induced Hypoprothrombinemia*

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THE WIDER CLINICAL application of hypoprothrombinemia-inducing anticoagulants has increased the need for a readily available antidote. At present, phytonadione (or oil soluble vitamin K_1) is accepted as an effective antidote to such drug-induced hypoprothrombinemia.[1,2] It is administered orally in doses ranging from 10 to 50 mg., or parenterally as an oil in water emulsion administered intravenously, usually in a 50 mg. dose. This oil emulsion has definite disadvantages, however. The stability of the emulsion may be "broken" by freezing or by mixing with numerous types of parenteral medicaments. Moreover, prolonged storage under less than ideal conditions is not recommended. The preparation must be diluted before it can be injected intravenously; yet despite such precautions, near syncopal and syncopal episodes sometimes follow.

A water soluble salt of phytonadione, dihydrovitamin K_1 biphosphate, recently was investigated in this laboratory in the hope that it would be an improvement over the emulsion. However, it proved to be a far less potent antidote under clinical conditions.[3] More recently, a microsuspension of vitamin K_1 has been made available. The oil soluble vitamin is in colloidal dispersion and is a clear amber fluid without visible particles containing 10 mg. per cc. of vitamin K_1 in an isotonic solution with benzyl alcohol as a preservative.

METHOD

The studies were performed successfully upon forty-eight adults who previously had been receiving anticoagulant therapy with bishydroxycoumarin (Dicumarol®) for actual or threatened thromboembolic phenomena. Forty of this group were hospitalized for acute myocardial infarctions, five for acute coronary insufficiency, two for acute pulmonary infarction and one for priapism. Blood prothrombin times were determined daily. The administration of bishydroxycoumarin was discontinued the day before testing, usually after the prothrombin time had been stabilized for several weeks at twenty-three seconds (50 per cent) or more. On the morning of the day of testing, determination of the prothrombin time was done just prior to the administration of colloidally suspended K_1† and two, four, six, eight and twenty-four hours thereafter. The initial prothrombin time in all subjects successfully tested was twenty-three seconds or higher. Eight subjects were used as controls. Each dosage and route was tested in a separate group of ten patients. The series included the administration of 10 mg. of the vitamin intravenously, intramuscularly or subcutaneously, plus one other group given 5 mg. intravenously. The vitamin also was used for the emergency treatment of single bleeding episodes in nine subjects (four of whom were also included in the series given 10 mg. intravenously). Seven subjects were given 10 mg. of phytonadione intravenously; one received the first 5 mg. intravenously followed by 10 mg. the following day; and one subject received 10 mg. subcutaneously. Oxalated blood was used throughout and the prothrombin times were determined by the Link-Shapiro modification of the Quick method, using SoluPlastin®

† AquaMephyton,® kindly supplied by Nathaniel S. Ritter, M.D., of the Department of Medical Research, Research Laboratories, Merck Sharp & Dohme, Inc., Rahway, New Jersey.

* From the Department of Medicine, Beth Israel Hospital, Newark, N. J. Aided by a grant from Merck, Sharp & Dohme, Inc., to the Research Foundation of the Beth Israel Hospital.

(solution of thromboplastin derived from fresh brain and lung tissue).

Results

Table I charts the results after the parenteral administration of 10 mg. intravenously, intramuscularly and subcutaneously and 5 mg. intravenously. The individual control prothrombin time in seconds was used as the baseline value; deviations from this value were averaged as mean positive or negative values. For example, a fall in prothrombin time of five seconds is recorded as −5 and a rise of eight seconds as +8. The bishydroxycoumarin was discontinued for twenty-four hours prior to testing; therefore, a moderate fall in the prothrombin times over the succeeding twenty-four hours after the last dose of anticoagulant is to be expected in the control series of eight subjects. In this trial, the mean fall after twenty-four hours was ten seconds. A potent vitamin K_1 should accelerate significantly this fall toward normal levels.

The 10 mg. intravenous dose was effective in reducing the elevated prothrombin times. A positive and statistically significant effect was noted two hours after injection, becoming maximum in four to six hours. P values of over 2.5 were found with each determination. However, this same dose when given intramuscularly was far less effective, requiring eight hours to begin to accelerate the fall of prothrombin time over the control values. These depressions were intermediate between those observed for the control and 10 mg. intravenous dose, and were maximum by the twenty-four hour observation. However, no statistical significance could be confirmed for these trials, despite this apparent trend. The 10 mg. dose given subcutaneously and the 5 mg. dose given intravenously showed no demonstrable effect over the control observations.

Despite the accelerated return to normal limits noted after giving 10 mg. intravenously and intramuscularly, four subjects of the former group and five of the latter group had prothrombin values of less than 50 per cent of normal twenty-four hours after the administration of vitamin K_1 confirming a definite persistence of anticoagulant effect. All of the subjects given 10 mg. of the drug intravenously had a fall in their prothrombin times. Three of those given the drug intramuscularly, however, had no fall whatsoever over the twenty-four hours of observation.

Table I

Response of Bishydroxycoumarin-Induced Hypoprothrombinemia to Parenterally Administered Colloidally Suspended Phytonadione (Vitamin K_1)

Time Observed (hours)	Mean Fall (seconds)	Standard Deviation from Mean	Minimum Fall (seconds)	Maximum Fall (seconds)
Control (eight subjects)				
2	2	3	(+) 3	9
4	3	2	(+) 3	7
6	5	4	2	9
8	6	4	0	10
24	10	6	0	23
10 mg. Given Intravenously (ten subjects)				
2	14	10	0	34
4	24	9	12	38
6	29	10	12	42
8	27	12	5	42
24	24	14	5	40
10 mg. Given Intramuscularly (ten subjects)				
2	7	11	(+) 4	35
4	7	12	(+) 3	37
6	10	13	(+) 8	37
8	10	11	0	37
24	18	15	0	45
10 mg. Given Subcutaneously (ten subjects)				
2	3	2	0	8
4	4	4	0	11
6	6	4	5	7
8	13	4	(+) 5	12
24	12	8	1	23
5 mg. Given Intravenously (ten subjects)				
2	2	4	(+) 6	8
4	5	3	(+) 5	12
6	6	3	2	11
8	7	5	1	12
24	11	5	(+) 11	18

Effect on Patients with Bleeding: Table II summarizes the data on those subjects treated for bleeding. Fortunately, no catastrophic hemorrhage occurred during these observations; gross hematuria was the most frequent hemorrhagic complication treated. All seven patients given the 10 mg. intravenously and the one patient given 10 mg. subcutaneously responded

TABLE II

Response of Bleeding Phenomena to Parenterally Administered Colloidally Suspended Phytonadione

Dose (mg.)	Route	Bleeding Phenomena	Time of Bleeding Control (hours)
10	Intravenous	Gross hematuria	12
10	Intravenous	Gross hematuria	6
10	Intravenous	Gross hematuria	8
10	Intravenous	Gross hematuria	18
10	Intravenous	Gross hematuria	9
10	Intravenous	Rectal	12
10	Intravenous	Pleural	24
10	Subcutaneous	Gross hematuria	6
5	Intravenous	Gross hematuria	Uncontrolled; responded to 10 mg. intravenously

well and within twenty-four hours or less. The single subject given 5 mg. intravenously for gross hematuria did not stop bleeding. His prothrombin time at the onset of bleeding was sixty-five seconds; twenty-four hours after this injection it was forty-five seconds, with the brisk bleeding unchecked. He then was given 10 mg. intravenously with an excellent response within twenty-four hours.

Adverse Reactions: No untoward reactions ascribable to the vitamin K_1 were experienced in any of these subjects. No special or unusual precautions were taken for its parenteral administration. It was given undiluted by all routes and no objective reactions were observed; there were no unusual patient complaints.

One patient died of a presumed pulmonary embolus six hours after receiving 10 mg. intravenously. Another patient sustained an extension of his myocardial infarction twenty-four hours after receiving a 10 mg. intramuscular dose. These episodes probably had no relation to the medication used, as they are frequent complications of the presenting illnesses under treatment.

COMMENTS

The effectiveness of the low dosage levels with hits newer preparation of phytonadione is demonstrated by the excellent clinical response of the bleeding episodes treated (Table II). All seven of the subjects who received 10 mg. intravenously and the one who received 10 mg. subcutaneously responded rapidly and without a recurrence of the bleeding. However, this small series should not give a sense of false confidence. Again, it should be emphasized that four of the subjects who were given 10 mg. intravenously did not reach a therapeutically safe prothrombin time level of 50 per cent or more even twenty-four hours after this dose was given. The intramuscular or subcutaneous routes offer an even less predictable assurance of success, although it appears that the intramuscular route may be utilized if a vein cannot be entered. In the therapy of catastrophic and life-threatening hemorrhage, one must still be prepared for failure. If, after an adequate trial of vitamin K_1 therapy, the prothrombin time fails to show a recovery one must then resort to transfusions of fresh blood to restore a normal coagulation mechanism and to reduce the elevated prothrombin time.

SUMMARY

A study of the effectiveness of a phytonadione (vitamin K_1) colloidal suspension in reducing the elevated prothrombin times of bishydroxycoumarin-treated patients was performed. Prothrombin times were studied two, four, six, eight and twenty-four hours after the administering to groups of ten patients each, of 10 mg. of the phytonadione intravenously, intramuscularly and subcutaneously, as well as after administering 5 mg. intravenously.

The 10 mg. dose given intravenously showed a statistically significant acceleration of the return of the elevated prothrombin times toward normal as compared to a control group of eight patients similarly studied. This effect was observed at two hours and was greatest four hours after the vitamin was given. The 10 mg. subcutaneous dose and the 5 mg. intravenous dose failed to accelerate the return of the prothrombin times toward normal. The 10 mg. dose given intramuscularly showed some effect after twenty-four hours, but this could not be proved statistically significant. Using the 50 per cent prothrombin time value as the index of a return to a normal coagulation mechanism, four out of the group of ten patients given 10 mg. intravenously failed to reach this value.

Nine bleeding episodes secondary to bishydroxycoumarin therapy were treated. Seven

patients receiving 10 mg. intravenously and one who received 10 mg. subcutaneously stopped their bleeding in six to twenty-four hours after treatment. The one patient who received 5 mg. intravenously continued to bleed until a second dose of 10 mg. was given intravenously.

References

1. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, p. 505. Philadelphia, 1956. J. B. Lippincott Co.
2. Newcomb, T. F. Current concepts in therapy: anticoagulants. *New England J. Med.*, 260: 545, 1959.
3. Shoshkes, M. and Tami, M. Dihydrovitamin K_1 biphosphate in bishydroxycoumarin-induced hypoprothrombinemia. *J. Lab. & Clin. Med.*, 46: 21, 1960.
4. Shoshkes, M. and Perelman, A. J. Vitamin K_1 in treatment of bishydroxycoumarin-induced hypoprothrombinemia: comparison of intravenous and intramuscular administration. *J.A.M.A.*, 161: 1145, 1956.

Review

Adams-Stokes Syndrome

A Review and Follow-up Study of Forty-two Cases*

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CURRENT OPINIONS differ concerning the exact definition of Adams-Stokes syndrome. Most authors include in the syndrome, fainting caused by too low a cardiac output caused either by too slow or too rapid ventricular activity. Parkinson et al.[1] applied the term Stokes-Adams disease to patients with heart block who suffer from attacks of unconsciousness due to a ventricular arrhythmia. I believe the best definition, taking into consideration both historic facts and clinical practices, is as follows: attacks of acute cerebral ischemia in nonanesthetized patients on the basis of a sudden change in cardiac rhythm. The cerebral ischemia can cause symptoms varying from unconsciousness with or without convulsions to just a slight dizziness or faintness. The arrhythmias can vary widely. Complete or partial heart block during the free periods is common but not necessary for the diagnosis.

According to this definition of Adams-Stokes syndrome, all degrees of cerebral ischemia are included. Some authors include only patients showing fainting or deep unconsciousness. However, there is a continuous transition from the slightest ischemia causing transitory dizziness to a very marked one producing unconsiousness. In all these cases the pathophysiologic mechanism is similar and there is no reason to set a certain limit such as fainting. Furthermore, in his book "The Diseases of the Heart and the Aorta," Stokes[2] apparently included all degrees of cerebral ischemia when writing: "In some there is a momentary unsteadiness in walking, and in others a tendency to faint . . . ; while in the more decided cases the patient becomes suddenly comatose."

Historical Notes on Terminology: About half a century after the descriptions by Adams[3] and Stokes,[2] Huchard proposed the name "Adams disease," apparently because of priority, or Stokes-Adams disease. This word sequence is surprising and Huchard did not motivate putting the name of Stokes before that of Adams. Stokes' description is more detailed than that of Adams and he also proposed the correct etiologic explanation. On the other hand, the sequence Adams-Stokes seems to be as common as the reverse one and it takes into consideration the fact that Adams' paper appeared earlier than Stokes'.

However, Adams[3] was not the first who described this syndrome. Morgagni gave a description in 1769.[4] The syndrome is also sometimes called Morgagni-Adams-Stokes syndrome. To be correct, however, one should then include all earlier descriptions in the name. If all earlier authors were to be honored by having their names included the name should at least be Gerbezius-Morgagni-Spens-Burnett-Adams-Stokes syndrome which is a little too long for practical use. Furthermore, Mayo,[5] Gibson,[6] Holberton[7] and Worthington[8] published descriptions during the time period between the appearance of the papers by Adams and Stokes. Further details on historic aspects are given in recent papers by MacMurray[9] and Lewis.[10]

INCIDENCE

It is impossible to get an exact appreciation of the incidence of Adams-Stokes syndrome in man because to be quite sure of the diagnosis it is necessary to observe the pulse during an attack. This is seldom possible and the doctor has only anamnestic reports on which to base his diagnosis. It is probable that a fainting attack in patients with a total heart block is in many cases an Adams-Stokes attack but this

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is not necessarily so. On two occasions I have been able to observe the cardiac activity in two patients with complete heart block during a syncopal attack. In one case the pulse did not change during the syncopal attack and in the other the electrocardiogram showed no cardiac arrhythmia. Adams-Stokes syndrome can never be diagnosed with certainty without at least palpation of the pulse during an attack.

The incidence of Adams-Stokes syndrome among patients* with complete heart block has been estimated differently. Hanssen[12] found forty-two in his material consisting of sixty-six patients with complete heart block during a ten year period and Hofmann[13] found Adams-Stokes attacks in 49 per cent of his patients with complete heart block. The corresponding figure for Fatzer[14] was 35 per cent and for Graybiel and White[15] about 66 per cent. Penton et al.[16] found syncope in 67 per cent of their patients with total heart block. Sheely[17] claimed that the incidence of Adams-Stokes attacks increases directly with increase in age.

Case Material: The present series consists of forty-two patients,† the total number of patients with a diagnosis of Adams-Stokes syndrome treated in the Malmö General Hospital during a ten year period from 1950 to 1959. Malmö is a town with slightly more than 200,000 inhabitants (1954) with one general hospital serving the whole population.

Table I shows the cases divided according to the age at the first Adams-Stokes attack. These figures are rather similar to those reported by Hanssen.[12] It is seen that Adams-Stokes syndrome is most frequent in the ages above fifty years. On the other hand, it is by no means exclusively restricted to the higher ages, for twelve patients had their first attack at an age below fifty years. There is an even sex distribution, twenty-three being men and nineteen being women, but in the higher ages there is a tendency for the number of men to predominate over that of women.

Three patients were hospitalized more than once (eight, seven and five times, respectively) because of the Adams-Stokes attacks; ten patients were hospitalized twice while the rest were hospitalized just once.

* Adams-Stokes syndrome is not exclusively a human disease; it has also been described in horses.[11]

† This is without doubt too low a figure because it includes only such patients who have been observed in an actual attack.

TABLE I

Forty-two Cases of Adams-Stokes Syndrome Classified According to Age at First Attack

Age at First Attack (yr.)	Number of Patients*		
	Male	Female	Total
0–20	2(0)	0(0)	2
21–30	0(0)	0(2)	2
31–40	1(0)	2(0)	3
41–50	1(1)	3(0)	5
51–60	2(1)	1(3)	7
61–70	3(2)	0(3)	8
71–80	2(4)	0(3)	9
>80	1(3)	1(1)	6
Total	12(11)	7(12)	42

* In this table and tables II, V and VI, the figures inside parenthesis indicate patients who were dead at the follow-up while the other figures indicate patients alive at the follow-up.

Etiologic Factors

Adams-Stokes syndrome has been ascribed to many causes. In his series of nineteen patients with Adams-Stokes syndrome, Hofmann[13] reported that complete heart block was produced by essential hypertension in eight cases, coronary artery disease in five, myocardial infarction in three, brown atrophy in one, mitral valvular disease in one and a gumma in the myocardium in another case. Gonin[18] listed the causes in decreasing order of frequency to be arterial lesions, mitral and aortic valvular disease and congenital lesions. Myocarditis of different etiologies was an infrequent factor. Among their patients with complete heart block Penton et al.[16] found syncope in 77.6 per cent of those with coronary artery disease and in 43, 72 and 38 per cent of those with acute myocardial infarction, hypertension and rheumatic heart disease, respectively. Robertson and Mathews[19] reported cases of Adams-Stokes syndrome caused by ventricular fibrillation and Kaindl and Rummelhardt[20] listed the causes of cardiac arrest or pronounced bradycardia producing Adams-Stokes attacks, including gumma, tumor, endocarditis, myocarditis and sclerotic changes.

Besides these reviews there are many case reports of Adams-Stokes syndrome due to various etiologic factors in addition to myocardial infarction, coronary artery disease, hypertension and rheumatic heart disease. These include cardiac catheterization,[21,22] congenital defects,[23–31c] rheumatic fever,[28,32–36] myocardi-

TABLE II
Classification of Cases According to Age at First Attack and Clinical Diagnosis

Age at First Attack (yr.)	Diagnosis									
	Coronary Heart Disease	Myocardial Infarction	Rheumatic Heart Disease	Hypertension	Myocarditis	Sarcoid	Bronchial Carcinoma	Chronic Nephritis and Myocardial Fibrosis	Gastroenteritis (?)	Cause Unknown
0–20	...	...	...	...	1	...	...	...	...	1
21–30	...	...	...	...	...	...	...	(1)	...	(1)
31–40	...	...	2	...	...	...	...	...	...	1
41–50	1	1 (1)	...	1	...	...	...	...	1	...
51–60	2 (2)	...	(1)	1	...	(1)	...	...	...	...
61–70	3 (1)	(2)	(1)	...	...	...	...	...	...	(1)
71–80	1 (5)	1 (1)	...	...	...	...	(1)	...	...	...
>80	2 (4)	...	...	...	...	...	...	...	...	...
Total	9 (12)	2 (4)	2 (2)	2	1	(1)	(1)	(1)	1	2 (2)

tis,[37] infection,[38–40] tumors,[41,42] sarcoidosis,[43–46] fibrosis of the A-V conduction system,[47–50] syphilis,[51,52] so-called Rytand's syndrome,*[53] calcified ventricular aneurysm,[54] amoebic hepatitis,[55] whooping cough[56] and drugs like quinidine,[19,57–59] prostigmine,[60] pilocarpine,[61] streptomycin,[62] potassium antimony tartrate[63] and digitalis.[64,65] A muscular type was described[66] but the existence of this type has been denied.[67] The neurogenic forms have been reviewed previously.[68] In some cases no obvious cause was found.[69,70]

Adams-Stokes attacks in children are comparatively rare but some cases have been described. The attacks have been ascribed to congenital complete heart block, rheumatic fever,[36,71] diphtheria,[72] acute hemorrhage[73] and congenital anomalies of various kinds.[24] Selander[74] states that cyanosis combined with cessation of heart sounds and breathing activity (which must be interpreted as an Adams-Stokes attack) is sometimes seen in infants, particularly immature ones.

Other precipitating factors described are acidosis and hyperkalemia,[75] swallowing,[68] touching of certain spots in the throat,[76,77] cholecystolithiasis,[78] emotions,[49,67,79–82] menstruation,[83] Aureomycin®[13] and Cardiazol.®[84] Schnur[85] believes that a partially inadequate vascular supply to the A-V bundle might result in total functional impairment without causing demonstrable histologic changes.

* This has been defined as fibrosis of the mitral annulus with involvement of the bundle of His, heart block and apical murmurs.

Clinical Diagnosis in Present Series: The different etiologic factors are listed in Table II which shows that coronary heart disease (in a few cases combined with valvular heart disease or essential hypertension) dominated. This is valid for both men and women. Next in frequency was myocardial infarction and, among women, valvular heart disease. In no case was there reason to suspect a luetic origin of the syndrome. The Wassermann reaction was made in twenty-seven cases and in no case was it positive. There was one case with Adams-Stokes attacks caused by sarcoidosis.

In this series there was a history of angina pectoris in three patients and mild cardiac insufficiency in four patients (Table III). Gallbladder disease including jaundice was found in eight patients. This is of great interest from a therapeutic point of view for cases have been described with an intimate relationship between gallbladder dysfunction and Adams-Stokes attacks.[78] Patients with Adams-Stokes attacks should, if possible, have an x-ray examination of their gallbladder and if there is any suspicion of a connection between the gallbladder disease and the Adams-Stokes attacks a cholecystectomy should be done.

It is worth mentioning that in the present material one patient had an infection of the throat and seven patients showed symptoms of acute infections, six of which were gastrointestinal, just prior to the appearance of the Adams-Stokes attacks. In one of these (Case 3) there was a definite connection between the

TABLE III
Associated Diseases and Symptoms

Associated Diseases	Number of Patients
Noncardiac diseases	
Cholelithiasis and icterus	8
Gastrointestinal disturbances	6
Diabetes mellitus	3
Commotio cerebri	3
Esophageal diverticulum	2
Cardiac symptoms	
Cardiac insufficiency (usually slight)	4
Angina pectoris	3

Adams-Stokes attacks and the gastrointestinal symptoms.

Three of the patients had diabetes mellitus and in two there was found an esophageal diverticulum at autopsy. One of these cases has been described in detail.[68] Two patients in whom no definite etiology for the attacks was found had sustained cerebral concussion earlier in their lives. One of these patients had had five concussions one of which was combined with a fracture of the skull (Table III).

ILLUSTRATIVE CASES

CASE 1. *Sarcoidosis of Myocardium:* A woman, fifty-eight years old, who had been well except for migraine and a ventricular ulcer experienced her first fainting attack three weeks before her admittance to the hospital. In the medical clinic there was found a complete heart block which changed to a sinus rhythm with a normal P-R interval and right bundle branch block. A roentgenogram of the heart and lungs was within normal limits. Serum cholesterol was 340 mg. per cent and the sedimentation rate 12 to 16 mm. per hour. The tuberculin test (1 mg.) was negative. She was treated with atropine, ephedrine and sedatives and discharged. Two months later she died suddenly. *Autopsy* showed sarcoid changes with a pronounced involvement of the myocardium and especially the interventricular septum.

This case is instructive as it shows that a widely spread sarcoidosis causing complete heart block and Adams-Stokes attacks can exist without any obvious clinical signs of the disease.

CASE 2. *Possible Case of Rytand's Syndrome:* Another patient, aged sixty-eight, with an apical murmur, diabetes mellitus, hypertension and gallbladder disease, died suddenly after having had multiple Adams-Stokes attacks. *Autopsy* showed pronounced calcifications of both mitral valve leaflets progressing into the myocardial septum. This might possibly be regarded as a case of so-called Rytand's syndrome.

CASE 3. *Acute Gastrointestinal Infection:* This was a forty-eight year old woman with a history of frequent vomiting attacks since her youth. On November 11, 1956 she vomited a couple of times. Two days later she had a watery diarrhea which persisted until November 16, 1956. On November 21, 1956 she had an Adams-Stokes attack and she again had diarrhea. An electrocardiogram during an attack showed a ventricular tachycardia. On December 5, 1956 she had a long Adams-Stokes attack. After seven minutes a thoracotomy was performed; the heart was found asystolic. After cardiac massage* the heart began beating spontaneously and three and a half years after the accident she is fairly well.

CASE 4. *Cerebral Concussion; Sinus Arrest:* This was a twenty year old butcher who was said to faint whenever he saw blood. At the age of seven years he fell from his bicycle and probably fainted. In 1955 he was hospitalized because of fainting after vomiting and nausea. His right pupil was larger than his left one. However, a neurologic examination including electroencephalogram before and after injection of 50 per cent glucose, x-ray films of the skull and right-sided carotid angiography revealed nothing but a slight papilledema, which soon partly disappeared. The patient felt well until 1958 when he was hospitalized because of similar attacks of unconsciousness. An electrocardiogram during an attack showed a long period of sinus arrest. Before the fainting when the patient had prodromes of the coming attack the electrocardiogram was normal. A roentgenogram of the chest was normal. Neurologic examination revealed a pseudopapillitis which had been noted three years earlier. The patient was given atropine and after this he has experienced only a slight transient attack. It seems probable that in this case a cerebral impulse produced the attacks. In favor of this is the type of electrocardiographic changes (sinus arrest) and furthermore the fact that he had a feeling of an impending attack while the electrocardiogram was still normal.

CASE 5. *A-V Block and Adams-Stokes Syndrome of Unknown Cause:* This was a twenty-two year old primagravida who in connection with delivery two months before her hospitalization had an attack thought to have been eclamptic. She was admitted to the medical clinic because of a fainting attack. She had a complete heart block with QRS complexes sometimes showing right and sometimes left bundle branch block. A roentgenogram of the heart was normal. Serologic reactions were within normal limits. During the Adams-Stokes attack a rapid

* The cardiac massage was performed by Dr. H. Ryd.

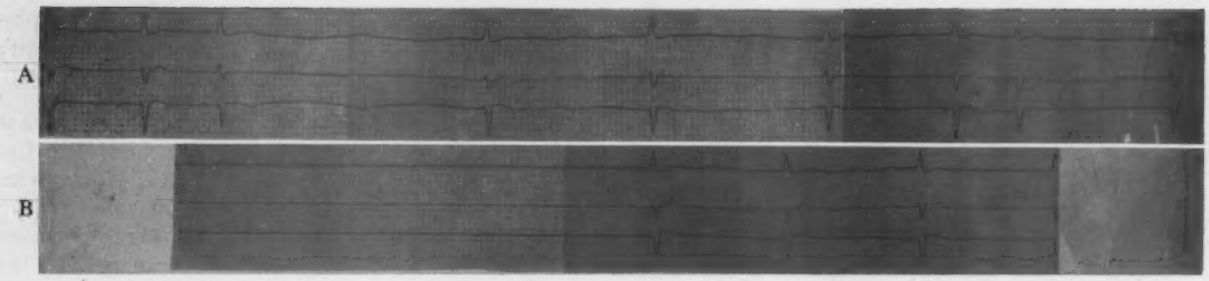

FIG. 1. Electrocardiogram. A, just before, and B, during an Adams-Stokes attack due to cardiac arrest.

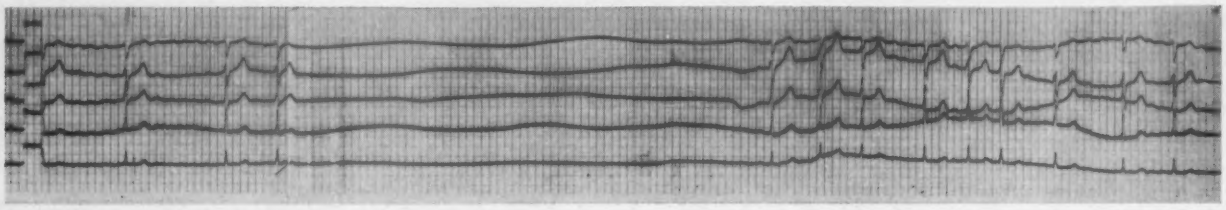

FIG. 2. Adams-Stokes attack due to cardiac arrest. The electrocardiogram just before the attack shows atrial fibrillation and the last ventricular complex before the attack is preceded by a P wave. The attack ends with a P wave, the rhythm later progressing into an atrial fibrillation.

cardiac activity was noted. She was given ACTH during eleven days with no beneficial effect. The case was clinically interpreted as a probable postpartum myocarditis. However, *autopsy and microscopic examination* of multiple slices from the conduction system and the myocardium showed no pathologic findings.

CLINICAL AND ELECTROCARDIOGRAPHIC NOTES

The clinical appearance of an Adams-Stokes attack displays a varying pattern. The mildest symptoms have been described as a momentary weakness or giddiness. The bystander may note a sudden pallor of the face and the patient may stop in the midst of a conversation or stagger.[86] In some attacks the loss of consciousness may be partial, in others a total loss of consciousness occurs with or without muscular twitchings or convulsions and passing of urine and stools. Characteristic is the initial pallor of the body and especially the face, in many cases gradually progressing into a cyanosis of increasing degree. When the heart starts beating and the pulse becomes palpable a sudden pink flush of the face occurs. The breathing during the attack is often stertorous; it may become gasping or cease at the end of an attack. Sometimes breathing of Cheyne-Stokes type is observed. Grassberger[49] described a certain type of breathing with increase in both depth and rate during the attack. Neuropathologic findings occur in the more serious and prolonged attacks such as conjugate deviation; the Babinski sign may be elicited. Focal neurologic phenomena have rarely been described.[86] In the present series a woman (Case 3) had cerebral damage and paralysis of the right arm after a prolonged Adams-Stokes attack.

Differentiation from Epileptic Fit: In some cases it is impossible to decide whether a patient with convulsions, loss of consciousness, passing of urine and stools and foam around the mouth has an Adams-Stokes attack or an epileptic fit. The best way to differentiate between these two diseases is palpation of the pulse during the attack. However, even this sign might be hard to evaluate as is demonstrated by a case reported by Krüskemper[87] in which the disappearance of the pulse occurred a few moments after the clouding of the sensorium. It is possible that Case 4 also belongs to this group. The case reported by Broser and Stühler[84]—a patient with attacks similar to petit mal and grand mal attacks, both beginning with an aura and which turned out to be no epileptic fits but Adams-Stokes attacks with asystole—is very instructive in this connection. An electroencephalogram in this patient showed no epileptic potentials. Gastaut and Fischer-Williams[88] have studied the *electroencephalographic pattern* in patients with syncope and concluded that while during epileptic fits the cortex is functioning this is not the case during a syncopal seizure. Bellville et al.[89] made similar studies of cardiac arrest during operation.

The Adams-Stokes attacks may be divided into a cardiogenic and a neurogenic form. The existence of the latter type has been questioned

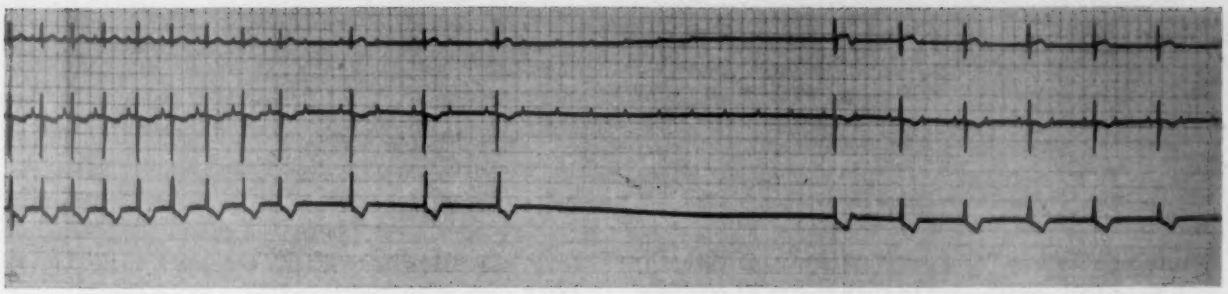

FIG. 3. Electrocardiographic changes after injection of 1×10^{-7} gm. acetylcholine into an isolated guinea pig heart perfused with Tyrode solution. Note the persistence of P waves and disappearance of the ventricular complexes. The P-R interval is but slightly prolonged and the P rate is essentially unchanged.

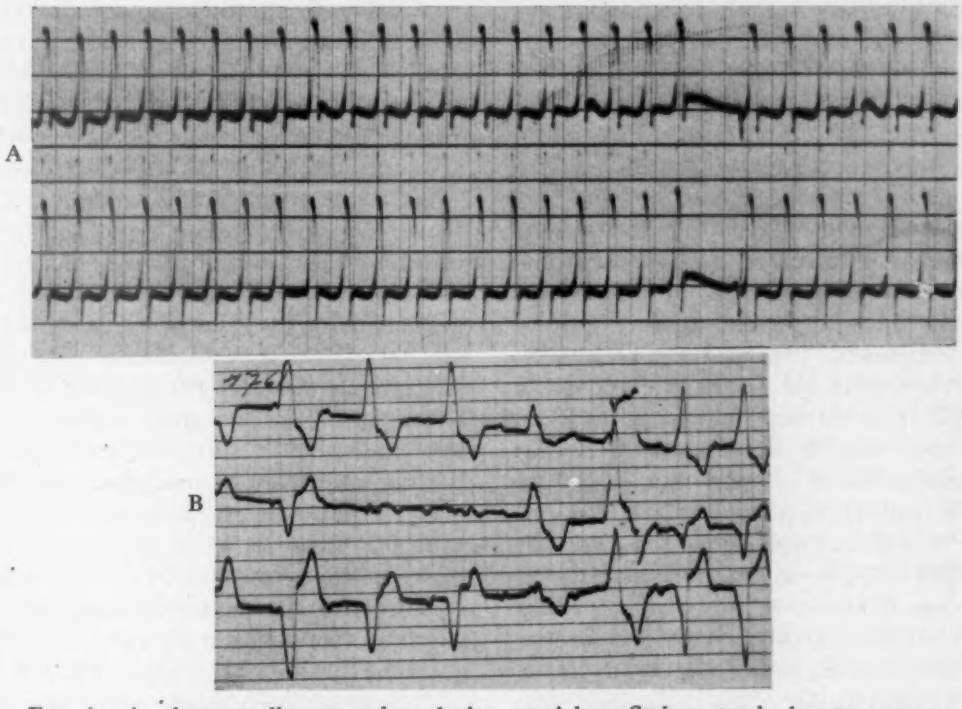

FIG. 4. A, electrocardiogram taken during an Adams-Stokes attack due to a supraventricular tachycardia. B, electrocardiogram just after the attack.

but I do not believe there is any doubt about the existence of a neurogenic form.[68,78]

ELECTROCARDIOGRAPHIC FEATURES

The electrocardiographic pattern described during an Adams-Stokes attack varies considerably. Holzmann[90] divided the attacks into (1) *adynamic forms* (Lähmungsform) which consist of (a) a ventricular adynamic form in which atrial activity is found and (b) a total adynamic form in which atrial activity is lacking; (2) *hypodynamic form* with a slow ventricular activity; (3) *hyperdynamic form* (Reizungsform) with too rapid cardiac activity.

Much has been written on Adams-Stokes attacks being due to a sinoatrial block (Fig. 1 and 2).[62,67,91–94] Attacks have, however, also been ascribed to ventricular standstil with remaining atrial activity (Fig. 3),[34,95] sinus bradycardia and other kinds of bradycardia,[54,61,66,96–99] paroxysmal supraventricular (Fig. 4)[100,104] and ventricular[101–103] tachycardia, or attacks of extrasystoles[104,105] sometimes in bigeminy,[105] ventricular flutter[83,106] and ventricular fibrillation (Fig. 5).[1,19,37,70,107–117] Various combined forms have also been described. The attacks may for example begin with a rapid phase (ventricular tachycardia or fibrillation) and end with ventricular asystole[23,56,85,118–120] or the reverse pattern is seen.[121,122] In some cases the palpated pulse is not only slow but also very irregular.[123,124] In Gluch's case[125] all the ventricular complexes were preceded by a P wave. He called this

FIG. 5. Electrocardiogram (lead V_4). A, just before, and B, during an Adams-Stokes attack due to ventricular fibrillation. The distance between two heavy lines is 0.1 second.

'sinus fibrillation." Combinations of different rapid forms (ventricular tachycardia, flutter and fibrillation) are also seen.[126–129] Hofmann[13] mentioned that Adams-Stokes attacks produced by atrial fibrillation with tachysystole are rare. Atrial flutter with too high a ventricular frequency has been reported.[104] Attacks combined with a strange form of monophasic action potential have been described by Schmidt.[130] Many of the previously mentioned arrhythmias have occurred without complete heart block having been registered.

Electrocardiogram during Attack: In the present series it was possible to record the electrocardiogram during an Adams-Stokes attack in sixteen patients. In four patients more than one attack was registered (Table IV). It is seen that tachyarrhythmias are almost as common as cardiac asystole and bradycardia. It is of interest to note that in the same patient the different Adams-Stokes attacks seemed to be caused by a similar cardiac arrhythmia. In three cases, which for various reasons have not been included in this series, the underlying arrhythmia was in one case ventricular fibrillation, in the second cardiac arrest and in the third case ventricular multifocal tachycardia followed by ventricular arrest. In this last case five attacks were recorded which all showed the same pattern.

Electrocardiogram in Interval between Attacks: An important question is whether it is possible from the electrocardiogram recorded during an attack-free interval to decide if the patient suffers from Adams-Stokes syndrome or some other form of attacks with similar symptoms. As previously stated it is my experience that in patients with complete heart block a syncopal episode must not necessarily mean an Adams-Stokes attack. Hofmann[79] claimed that in patients with A-V block a high atrial rate with equal P-P intervals and prolonged QRS duration are signs of a proneness to Adams-Stokes attacks while a low atrial rate, a pronounced Erlanger-Blackman phenomenon* and a normal QRS duration indicate that the patients are free from Adams-Stokes attacks. The value of bundle branch block as a sign supporting the diagnosis of Adams-Stokes syndrome has also been stressed by Stokes[131] and Bourne.[132] On the other hand, Broser and Stühler,[84] Schwartz and Hauswirth[115] and Cookson[133] have found a normal electrocardiogram between the attacks and Penton et al.[16] found that in many cases syncope may precede permanent complete heart block by months or a few years. Söderström[134] recorded conspicuously long R-R intervals in some patients with atrial fibrillation; these he considered to be in immediate danger of Adams-Stokes attacks. Schwartz and Hauswirth[115] found a certain type of ventricular oscillation to be pathognomonic for ventricular fibrillation.

TABLE IV

Cardiac Arrhythmias Recorded Electrocardiographically during Adams-Stokes Attack

Arrhythmia	Number of Patients	Number of Attacks
Ventricular fibrillation	4	4
Ventricular flutter or tachycardia	2	2
Cardiac arrest	5	7
Bradycardia	3	5
Ventricular tachyarrhythmia and cardiac arrest	2	2

In the present series it was found that complete heart block prevailed in sixteen cases in the interval between attacks, while sinus rhythm was found in nineteen cases, nodal rhythm in three cases and atrial fibrillation in four cases. It has been stated that the Q-T duration is prolonged after an attack. In the present series it occurred in only a few cases. Extrasystoles were often noted between attacks caused by a tachyarrhythmia but this was an occasional finding also in patients with Adams-Stokes attacks due to cardiac arrest.

In patients with complete heart block subject

* A positive Erlanger-Blackman phenomenon implies that in block the P-P intervals with a QRS complex are shorter than the P-P intervals without a QRS complex.

to Adams-Stokes attacks, the QRS duration was usually prolonged, the mean being 0.11 second. In three patients with a complete heart block and no Adams-Stokes attacks the QRS duration was within normal limits, the mean being 0.08 second. These results confirm those earlier published by Stokes,[131] Bourne[132] and Hofmann.[79] With these three patients as controls I have also tried to test the other criteria given by Hofmann.[79] It was found that the atrial rate averaged 97 per minute in patients with complete heart block and Adams-Stokes attacks and 78 per minute in patients without attacks. The Erlanger-Blackman phenomenon was found positive in one and negative in five patients with Adams-Stokes attacks and in patients without attacks positive in two, and negative in one. The figures are small but they seem to confirm Hofmann's results.

Mechanisms of Attacks

Sinus Arrest in Sinoatrial Block: It has been supposed that vagal influences might be of importance in producing sinoatrial block. Certain clinical experiences suggest that other factors are also of importance; it has been reported that atropine is of no[135] or little[79] value in this condition. Schild and Weise[136] proposed that changes in the autonomic innervation might be of importance in creating a sinoatrial block and Thomsen[135] found in his patient that sympathetic stimulation with exercise and amyl nitrite converted a slow irregular pulse to a regular pulse of normal rate. Some of these experiences might perhaps be interpreted to indicate that, in some cases at least, the eliciting factor is not an increased vagal tone but rather a decreased sympathetic tone. Christoffersen and Vermehren[137] considered it probable that the cardiac lesion producing the sinoatrial block is not limited to the sinus node, for this is large, but that the atria are involved too.

Ventricular Asystole and Bradyarrhythmia: Ventricular arrest combined with persistent atrial activity is more difficult to explain. Bellet et al.[75] have pointed out the different sensitivity to hyperkalemia of the ventricular pacemaker and the sinus node and also the importance of changes in pH for the precipitation of Adams-Stokes attacks. According to Wenckebach and Winterberg,[67] Schmoll[47] was the first to suppose that in patients with heart block the propagation of the impulse in the ventricles might be blocked, in this way producing an Adams-Stokes attack. Volhard[137] called this "block in block." The existence of this block in block mechanism is supported by an observation by White[138] who described a case with complete heart block where the ventricular rate alternated between 36 and 19 per minute. White supposed that sometimes every second beat emanating from the ventricular pacemaker was blocked. There are thus certain facts in favor of the view that the ventricular arrest combined with persisting atrial activity might be a pre-automatic pause because of blocking of the impulses emanating from the A-V node or the ventricle.

Vagal Factors: Besides the other factors involved (acidosis, hyperkalemia) it is possible that a vagal influence may be of some importance. There are certain facts favoring the view that the influence of the vagus on centers "below" the sinus node can be rather pronounced, at least under some conditions:

1. The shortening of the Q-T interval after vagal stimulation.

2. Clinical results such as the one reported by Hick[139] who observed ventricular arrest in a patient without partial block before and after the Adams-Stokes attack and with the atria beating regularly all the time. These attacks could be reproduced by carotid sinus pressure. I have also observed a case where there are reasons to believe that a vagal reflex produced ventricular arrest while the atria were still beating.[68]

3. Experimental results as shown in Figure 3.

Wenckebach and Winterberg[67] partially adopting a theory proposed by Erlanger[141] stated that in patients with partial heart block an Adams-Stokes attack can be produced by (1) development of a complete heart block; (2) increased inhibition of the conduction mediated through the vagus; and (3) an increase of the atrial rate.

There are other conceivable mechanisms in patients with Adams-Stokes attacks caused by a bradycardia, such as *changing blood supply to the sinus node*. To this group probably belong the cases reported by Bäumler,[142] Griffith[143] and Wenckebach and Winterberg[67] in which Adams-Stokes attacks appeared correlated to the different phases in Cheyne-Stokes breathing.

Ventricular Tachyarrhythmias: The mechanism behind the development of tachyarrhythmias is not clear. As for Adams-Stokes attacks caused by ventricular fibrillation in patients with acute myocardial infarction, Beck's theories[144] con-

cerning oxygen differential potentials are of interest.

Therapy

The earlier treatment of Adams-Stokes syndrome was rather simple. With the hypothesis that the attacks were caused by cardiac arrest or pronounced bradycardia the patients were given ephedrine, atropine or similar drugs. After it had been known that an attack can also be produced by a tachyarrhythmia therapy has in certain respects changed. It is most important always to have an electrocardiogram of an attack to know which is the underlying arrhythmia.

Adams-Stokes attacks appear very irregularly and because of this the result of the therapy is difficult to evaluate. Furthermore, most authors report a very small number of patients, making it very hard to compare different drugs or the effect of the same drug on different occasions. Zoll et al.[135] have shown that even during very similar experimental conditions there occur striking differences in effects of the same agent in closely spaced trials on the same patient.

Sometimes it is possible to determine the etiology of the Adams-Stokes syndrome. In these cases it is important to treat the underlying disease (treatment of syphilis, diphtheria, etc., surgical resection of an esophageal diverticulum or gallbladder, nerve section in some cases of the neurogenic form, cessation of a drug producing the attacks, etc.).

Sympathomimetic Amines: In attacks produced by ventricular arrest or pronounced bradycardia it is of importance to arouse new foci and increase the ventricular rate, respectively. For this purpose different sympathomimetic amines have been used. It has been stated[16] that only epinephrine, isoproterenol, (Isuprel,® isopropylnorepinephrine) and ephedrine show a stimulating effect high enough while other sympathomimetic amines are of less or no value for this purpose.[16] Zoll et al.[145] found the effects of epinephrine and isoproterenol to be similar except in their effects on the blood pressure and on the sinoatrial rate. Epinephrine tended to increase the blood pressure while isoproterenol had either no effect or decreased the blood pressure. Isoproterenol usually accelerated the sinoatrial rate markedly, whereas the effect of epinephrine was comparatively slight.

Isoproterenol mainly affects the higher cardiac centers like the S-A and A-V nodes. This is the reason why isoproterenol has been recommended even when extrasystoles occur[117] or when ventricular arrest alternates with ventricular tachycardia or fibrillation in the same patient. After subcutaneous administration the effect of isoproterenol appears earlier and reaches a peak earlier than epinephrine.[146] Isoproterenol can be administrated sublingually, subcutaneously, intramuscularly or intravenously. The intravenous route is not without risks and should be used only in urgent cases. The effect is rapid even with a sublingual administration. It is often necessary to use rather high doses (10 to 20 mg. every one to six hours). Norepinephrine has been said to produce ectopic rhythms. It is my experience from animal experiments that there is no difference between epinephrine and norepinephrine in the production of ventricular extrasystoles.

Other Drugs: In some cases atropine is of value especially when there are reasons to suspect a neurogenic origin.[95,124] In some of these cases of neurogenic origin it has been possible to abolish the attacks by sectioning the pertinent nerve.[68,123,147] Bellet[148] holds molar sodium lactate to be an extremely valuable adjunct in the treatment of Adams-Stokes attacks, especially those produced by cardiac arrest. This agent has also been used by other authors, not always with the good results Bellet has reported.[45,145,149] Barium chloride has been advocated as a stimulating agent.[150–152] It is used to a rather small extent now as for different reasons it is regarded as potentially dangerous.[153,154] There is no unanimous opinion concerning the use of digitalis.[20,155] Other drugs recommended are thyroxin,[156] Paredrine,®[28] Pervitin,®[136] caffein,[136] corhormon,[157] ethylnorepinephrine,[54] benzedrine,[158] methamphetamine[158] and hypertonic glucose solution.[159] These agents have been tried on a small number of patients only and the results are difficult to evaluate.

Artificial Electrical Pacemakers: In 1951 Callaghan and Bigelow[160] described the use of an electrical artificial pacemaker for standstill of the heart of dogs and rabbits. Zoll[161] in 1952 published a report on the use of an external pacemaker in man. The indications have been developed by Zoll and many other reports on the use of electrical artificial pacemakers have appeared.[145,162–165] The technic has varied somewhat: Some authors used external stimulation; Furman and Schwedel[166] stimulated the endocardium of the heart through a catheter; Others implanted a myocardial wire or

electrode percutaneously or by epicardial suture. Jackson et al.[167] described a patient who learned to manage the pacemaker himself, turning it on when he felt the attack was coming. One of the difficulties is that after some time the stimulation threshold becomes too high. I have tried to overcome this difficulty by using a transistor pacemaker which is automatically turned on when the heart stops beating and stops itself when the heart again begins beating.

Another method that seems very promising has been developed by Elmquist.[168] He has avoided the gradually increasing resistance by constructing an electrode consisting of a thin platinum disk of an area of about 1 square cm. attached to a piece of plastic. Through two holes the electrode can be sutured to the epicardium. By this method an electrode has been functioning one and a half years without increase in the resistance.[169] The wires go from the electrodes to the generator which is implanted subcutaneously. Further experiments with this type of electrode are in progress in the Cardiological Laboratory in Malmö and our experience of it is good. When, at an emergency, it becomes necessary artificially to stimulate the heart this electrode of course cannot be used. In these cases the heart should be stimulated externally or punctured with a needle being in communication with a wire and stimulator. This equipment should be easily available in an emergency department. Another method that seems promising is the external cardiac massage.

Ventricular Tachycardia and Fibrilation: In Adams-Stokes syndrome caused by a tachyarrhythmia quinidine, procaine amide and sometimes potassium have been used.[16,101,170] It has been pointed out, however, that these agents are contraindicated in patients with complete heart block[16,171,172] and quinidine seemed to aggravate the state in the presence of intraventricular conduction defects.[19] Zoll et al.[172] stated that this contraindication does not apply to patients with partial A-V block. Schwartz et al.[171] ascribed the contraindications to the following characteristics of the procaine amide: depressant effects on the S-A and A-V nodes and on the conduction within the ventricles. Furthermore, this drug favored the development of ventricular ectopic beats progressing into ventricular fibrillation. Zwillinger[127] obtained good results by injection intracardially of 10 to 20 cc. of a 15 per cent solution of magnesium sulfate. Winter[81] reported a patient whose attacks were precipitated by mental excitement. In this patient quinidine had no effect while morphine and a barbiturate in large doses prohibited the attacks. In a patient with attacks produced by ventricular fibrillation progressing into ventricular arrest Levine and Matton[118] reported a good effect of epinephrine during the second phase. It has been possible to stop ventricular fibrillation with alternating current.[173] Sometimes thoracotomy becomes necessary[174] as was performed on one patient in the present series.

Steroid Therapy: ACTH and corticosteroids have been used in the treatment of Adams-Stokes attacks with varying degree of success. Prinzmetal and Kennamer[175] in 1954 described its use in acute myocardial infarction. Friedberg et al.[176] reviewed the literature and reported its use also in chronic cases in which there was no suspicion of recent myocardial infarction or inflammatory infiltrations.

In some cases the exact arrhythmia causing the Adams-Stokes attack is not known. In these cases it has been recommended to give isoproterenol.[16,117]

It is difficult from the present series to evaluate the superiority of one special remedy over another. It might be of interest, however, that as early as 1955 a patient with Adams-Stokes attacks (Case 5) was treated with ACTH but with no apparent beneficial effect. We have later used steroids or ACTH in a few patients, in some without effect and in some probably with at least a transitory decrease or disappearance of the Adams-Stokes attacks.

Prognosis

The prognosis of a patient with Adams-Stokes attacks is usually regarded as very bad. This, however, is not necessarily so. It is conceivable that the attacks will decrease in number or disappear completely when the underlying mechanism is broken.[61,68,78,124,147,177,178,179] Adams-Stokes attacks complicating congenital heart block are said to have a good prognosis.[30,31] This is also the case for attacks which are said to be produced by an overactivity of the vagus.[97,180] Sinoatrial block causing Adams-Stokes attacks usually has a good prognosis[13,67,135] even if all authors do not agree.[94,181] Dressler[126] regarded ventricular fibrillation as prognostically more unfavorable than ventricular arrest. Bellet[148] held the prognosis to be better in those cases in which normal sinus rhythm followed the complete block.

Most of the previously mentioned results are

TABLE V
Survival Time after First Attack According to Clinical Diagnosis

Diagnosis	Number of Patients Surviving First Attack (yr.)				
	<1	1–3	3–5	5–10	>10
Coronary heart disease	2 (9)	1 (1)	1 (1)	3 (1)	2
Myocardial infarction	1 (4)	...	...	...	1
Sarcoid	(1)	...	...	...	...
Valvular heart disease	(1)	...	(1)	2	...
Hypertension	...	...	...	...	2
Bronchial carcinoma and esophageal diverticulum	(1)	...	...	...	...
Chronic nephritis and myocardial infarction	(1)	...	...	...	...
Myocarditis	...	...	...	...	1
Gastroenteritis (?)	...	...	1	...	...
Unknown cause	(1)	(1)	...	2	...

derived from causistic reports. In forty-two patients with Adams-Stokes syndrome described by Hanssen[12] a rather high mortality was observed during the first observation year in patients more than sixty years old. Penton et al.[16] claimed a bad prognosis for patients who had Adams-Stokes attacks for the first time during an acute myocardial infarction. The average duration of life after the first syncopal attack in cases other than those just mentioned was about seven years, the range being from several hours to eleven years. Robertson and Mathews[19] arrived at a similar conclusion, stating that the prognosis is always grave but it is significant that survival for years is possible.

Survival in Present Series: In the present series there were at the follow-up nineteen patients alive while twenty-three had died. Table V shows the time of survival after the first attack divided according to the diagnosis. Patients with coronary heart disease form the largest group. There was a high mortality during the year after the first attack. However, about half the patients survived more than one year and two have survived ten years or more (ten and twenty-five years, respectively). The present material confirms the observation by Penton et al.[16] that the prognosis for Adams-Stokes attacks in patients with myocardial infarction is bad, with four patients out of six dead within the first year. On the other hand, one patient has survived for eleven years and the one still alive at the follow-up was in good condition five months after his infarction.

TABLE VI
Survival Time with Reference to Age at First Attack

Age at First Attack (yr.)	Number of Patients Surviving First Attack (yr.)				
	<1	1–3	3–5	5–10	>10
0–20	...	...	...	1	1
21–30	(2)	...	...	...	...
31–40	...	...	...	3	...
41–50	1 (1)	...	1	1	1
51–60	(3)	...	(1)	1	2
61–70	(4)	(1)	1	1	1
71–80	(5)	1 (1)	(1)	...	1
>80	2 (3)	...	...	(1)	...

TABLE VII
Status of Patients Who Survived First Adams-Stokes Attack

Status	Number of Patients
Reduced heart volume	
<500 cc.	10
500–800 cc.	7
>800 cc.	1
No data	1
Symptoms	
No symptoms	1
Moderate symptoms (can work)	9
Pronounced symptoms (cannot work)	9
Change in fitness for work	
No change	15
Moderate decrease	3
Invalided	1

Table VI shows the survival time related to the age at the first attack. The cause of death in twenty-three patients was as follows: (1) Adams-Stokes attack in ten patients; (2) other diseases in six patients; and (3) unknown in seven patients. It is apparent that the death of many patients coincides with a new Adams-Stokes attack. In only two cases surviving more than one year has it been possible to decide the cause of death: both these patients died after an Adams-Stokes attack.

Cardiac Status in Surviving Patients: Table

TABLE VIII
Prevailing Cardiac Mechanism Between Attacks

Status at Follow-up Study	Prevailing Rhythm between Attacks				Normal QRS-Duration	Bundle Branch Block
	Sinus Rhythm	Nodal Rhythm	Auricular Fibrillation	Complete Heart block		
Surviving	9	1	4	5	14	5
Dead	10	2	0	11	8	15

VII shows that almost all the surviving patients have some symptoms of their disease although about half of them can work. Most of these patients' symptoms are caused by the underlying disease; they are not sequelae of the Adams-Stokes attacks. This is apparent from the table which shows that in fifteen out of nineteen patients there was no change in their ability to work after the attacks began. Table VII also shows that more than half of the surviving patients have a normal heart size on roentgenography.

Five of the nineteen surviving patients showed occasional or constant bundle branch block, usually left-sided, while no bundle branch block was found in fourteen patients; corresponding figures among the twenty-three dead patients were fifteen and eight (Table VIII). Sinus rhythm prevailed in nine surviving patients while five showed a complete heart block, four atrial fibrillation and one patient had a nodal rhythm. Eleven of the dead patients showed a complete heart block—in two sometimes interrupted by sinus rhythm—two had a nodal rhythm and ten showed sinus rhythm; in about half of these ten cases blocks of different degree were found. Extrasystoles were seldom seen in the survivors but occurred frequently in the patients dead at the follow-up. Table IX shows that the tachyarrhythmic forms of Adams-Stokes attacks did not have a worse prognosis than those caused by bradycardia or cardiac arrest. Two patients not included in this series had Adams-Stokes attacks caused by cardiac arrest and bradycardia, respectively. Both patients died within the first year after the attacks began.

TABLE IX
Cardiac Mechanism during Attack and Survival Time

Type of Arrhythmia during Adams-Stokes Attack	Number of Patients Surviving First Attack (yr.)				
	<1	1–3	3–5	5–10	>10
Ventricular fibrillation and flutter	2	1	1	...	2
Ventricular tachycardia	1	...	...	...	...
Bradycardia	2	...	...	...	...
Cardiac arrest	5	...	1	1	...

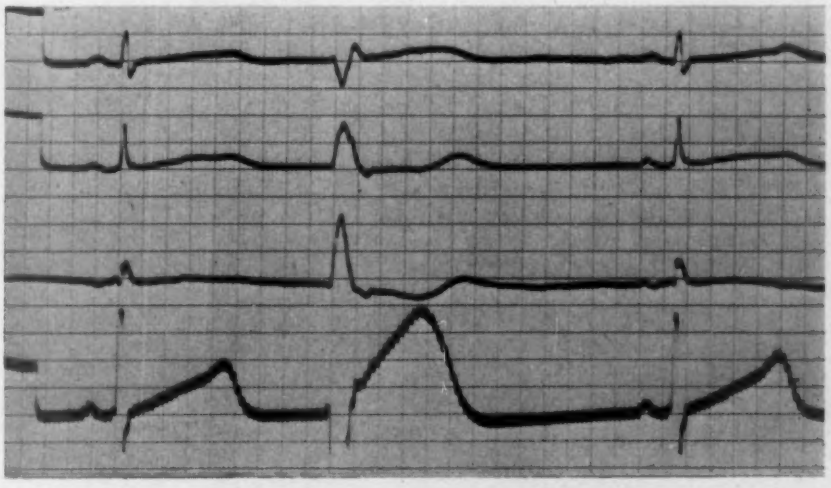

FIG. 6. Case 6. Electrocardiogram at eight years of age.

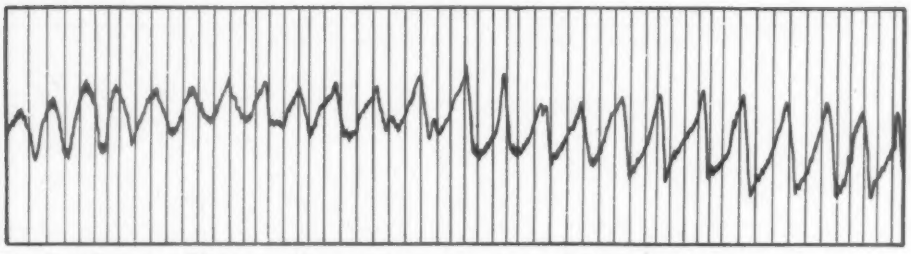

FIG. 7. Case 6. Electrocardiogram during an Adams-Stokes attack, showing ventricular tachycardia or fibrillation.

The following case report also shows that even if ventricular fibrillation produces the Adams-Stokes attacks, the prognosis need not be grave.

CASE 6. *Survival Following Adams-Stokes Attacks Due to Ventricular Fibrillation:** This was a twenty-six year old man who had pneumonia twice in his youth and as a child had whooping cough and measles. At the age of five, syncopal attacks began. They appeared during sleep or in the morning. They were thought to be of an epileptic nature although electroencephalograms showed no signs of epilepsy. At eight years of age he was hospitalized with a diagnosis of acute encephalitis, acute myocarditis and epilepsy. Auscultation revealed an apical systolic murmur. Repeated electrocardiograms showed a strange pattern with broad T waves and a marked Q-T prolongation (Fig. 6). There is a possibility that the "Q-T" prolongation is produced by a U wave. If this is so the U wave is of an abnormally high amplitude. At age twenty years the electrocardiographic pattern was the same. Injection of calcium chloride and magnesium sulphate intravenously and an exercise test did not change the pattern; nor did potassium acetate by mouth. Values for serum potassium, calcium, sodium and phosphorus were normal. X-ray examination of the heart showed a normal configuration but it was slightly enlarged. This enlargement had disappeared at the follow-up examination.

During hospitalization at sixteen years of age a syncopal attack was registered electrocardiographically and showed in the beginning a ventricular fibrillation and in a later phase another type of arrhythmia which is more like a ventricular tachycardia (Fig. 7). At present the patient can work and feels well. The number of attacks has shown a tendency to decrease in frequency: during 1959 he had four attacks against ten per year earlier.

Frequency of Subsequent Attacks: There was most often a tendency to a decrease in the frequency of the Adams-Stokes attacks. Among the survivors the attacks had disappeared completely within the first year in four patients, within one to three years in six and within three to five years in two patients. On the other hand, in seven out of the nineteen surviving patients the attacks never ceased. Three patients with a follow-up of five to ten years had one to fifteen, ten to thirty and more than thirty attacks per year, respectively. In four patients with a follow-up of more than ten years, one patient had six to ten, two had ten to thirty and one patient had more than thirty attacks per year.

* This patient has been reported by Dr. Belfrage at the Meeting of the Swedish Medical Association, 1958.

SUMMARY

A review of the literature on Adams-Stokes syndrome is given and a series of cases from the General Hospital in Malmö during a ten year period is presented. The series consists of forty-two patients and includes only such patients in whom an attack has been observed.

Adams-Stokes syndrome is most frequent above fifty years of age but about 30 per cent of the patients had their first attack below fifty. Coronary heart disease dominated as an etiologic factor; next came myocardial infarction and, among women, valvular heart disease. Some case reports are given, one of Adams-Stokes attacks caused by sarcoid, another by Rytand's syndrome.

It was possible to record the electrocardiogram during an Adams-Stokes attack in sixteen patients. When more than one attack was registered in the same patient the different attacks seemed to be caused by a similar cardiac arrhythmia. A tachyarrhythmia produced the attacks almost as often as a bradycardia or asystole. In patients with complete heart block it was found that a syncopal attack was more probably an Adams-Stokes attack if the QRS duration was prolonged, if the atrial rate was high and if the P-P intervals were equal.

The mechanisms precipitating the attacks are mentioned. It is suggested that a vagal influence on centers "below" the sinus node

might be of greater importance than believed earlier.

The prognosis for a patient with Adams-Stokes attacks is usually regarded as very bad. This, however, is not necessarily so. Patients with coronary heart disease show a high mortality during the year after the first attack but about half the patients survived more than one year and two have survived ten years or more. The prognosis for patients with Adams-Stokes attacks following myocardial infarction is bad, with four patients out of six dead within the first year. On the other hand, the prognosis need not be bad if the patients survive the first months. Bundle branch block and arrhythmias of different kind were found to be signs of bad prognosis. There was no difference in the prognosis of attacks produced by a bradyarrhythmia and a tachyarrhythmia.

References

1. Parkinson, J., Papp, C. and Evans, W. The electrocardiogram of the Stokes-Adams attack. *Brit. Heart J.*, 3: 171, 1941.
2. Stokes, W. The Diseases of the Heart and the Aorta, p. 323. Dublin, 1854. Hodges & Smith.
3. Adams, R. Cases of diseases of the heart accompanied with pathological observations. *Dublin Hosp. Rep. Communic. in Med. Surg.*, 4: 353, 1827.
4. Morgagni, J. B. The seats and causes of diseases, in: Major, R. H. Classic Descriptions of Disease, 3rd ed. Oxford, 1948. Blackwell Scientific Publications.
5. Mayo, H. Some cases of slowness of the pulse. *London M. Gaz.*, 22: 232, 1838.
6. Gibson, J. R. Cited in reference 9.
7. Holberton, T. H. A case of slow pulse with fainting fits which first came on two years after an injury of the neck from a fall. *Med. Chir. Trans. Roy. Soc., London*, 24: 76, 1841.
8. Worthington, W. C. Cited in reference 9.
9. MacMurray, F. G. Stokes-Adams disease. A historical review. *New England J. Med.*, 256: 643, 1957.
10. Lewis, J. K. Stokes-Adams disease. An account of important historical discoveries. *Arch. Int. Med.*, 101: 130, 1958.
11. Bang, O., Petersen, G. and Petersen, O. V. C. E. Two cases of bradycardia in horses. Adams-Stokes' disease. Sinus-bradycardia. *Heart*, 6: 199, 1917.
12. Hanssen, P. The incidence of auricular flutter and auricular fibrillation associated with complete auricular-ventricular dissociation. *Acta med. Scandinav.*, 136: 112, 1949.
13. Hofmann, H. Herzrhythmusstörungen bei Adams-Stokesschen Syndrom und ihre Behandlung. *Ztschr. ges. inn. Med.*, 10: 516, 1955.
14. Fatzer, G. Étude de l'electrocardiogramme dans le bloc atrio-ventriculaire. *Cardiologia*, 10: 305, 1946.
15. Graybiel, A. and White, P. D. Complete auricular-ventricular dissociation. A clinical study of seventy-two cases with a note on a curious form of auricular arrhythmia frequently observed. *Am. J. M. Sc.*, 192: 334, 1936.
16. Penton, G. B., Miller, H. and Levine, S. A. Some clinical features of complete heart block. *Circulation*, 13: 801, 1956.
17. Sheely, R. F. Adams-Stokes disease in the geriatric patient. *J. Am. Geriatrics Soc.*, 2: 223, 1954.
18. Gonin, A. Le syndrome de Morgagni-Adams-Stokes (vertiges et syncopes dans la dissociation auriculo-ventriculaire). *Arch. mal. coeur*, 31: 1172, 1938.
19. Robertson, E. S. and Mathews, E. C. Paroxysmal ventricular fibrillation producing Adams-Stokes syndrome. *Arch. Int. Med.*, 90: 320, 1952.
20. Kaindl, F. and Rummelhardt, K. Zur Therapie rezidivierender Adams-Stokes-Anfälle. *Wien. klin. Wchnschr.*, 68: 583, 1956.
21. Hall, P. Personal communication.
22. Sasahara, A. A., Rudolph, A. M., Hoffman, J. I. E. and Hauck, A. J. Ventricular fibrillation during catheterization of the right side of the heart terminated successfully by external defibrillation. *New England J. Med.*, 261: 26, 1959.
23. Clark, R. J. and White, P. D. Congenital aneurysmal defect of the membranous portion of the ventricular septum associated with heart block, ventricular flutter, Adams-Stokes syndrome and death. *Circulation*, 5: 725, 1952.
24. Faessler, B. Das Adams-Stokessche Syndrom im Säuglingsalter. *Ann. paediat.*, 153: 327, 1939.
25. Schaub, F., Holzmann, M. and Wyss, S. Zur Behandlung von Adams-Stokesschen Anfällen und Ueberleitungsstörungen des Herzens. *Schweiz. med. Wchnschr.*, 87: 938, 1957.
26. Connor, A. C., McFadden, J. I., Houston, B. J. and Finn, J. L. Familial congenital heart block. *Am. J. Obst. & Gynec.*, 78: 75, 1959.
27. Jaleski, T. C. and Morrison, E. T. Congenital heart block. A study of two cases in healthy adults. *Am. J. M. Sc.*, 206: 449, 1943.
28. Friedberg, C. K. Diseases of the Heart, pp. 730, 837. London, 1956. W. B. Saunders Co.
29. Keith, J. D., Rowe, R. D. and Vlad, P. Heart Disease in Infancy and Childhood, p. 830. New York, 1958. MacMillan Co.
30. Campbell, M. Congenital complete heart block. *Brit. Heart J.*, 5: 15, 1943.
31*a*. Campbell, M. and Thorne, M. G. Congenital heart block. *Brit. Heart J.*, 18: 90, 1956.
31*b*. Campbell, M. and Turner-Warwick, M. Two more families with cardiomegaly. *Brit. Heart J.*, 18: 393, 1956.
31*c*. Jervell, A. and Lange-Nielsen, F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. *Am. Heart J.*, 54: 59, 1957.
32. Salvesen, H. A. Complete heart block in the course of an acute rheumatic infection. *Acta med. Scandinav.*, 78: 189, 1932.
33. Gibson, T. C. and Hughes, J. P. Stokes-Adams attacks in acute rheumatic carditis. *Brit. Heart J.*, 18: 427, 1956.
34. Greene, J. A. and Bennett, A. W. Acute rheu-

matic heart disease in the aged, with report of a case with Stokes-Adams syndrome treated with paredrine. *Am. Heart J.*, 30: 415, 1945.
35. Faulkner, J. M. Adams-Stokes' syndrome in rheumatic fever; report of a case. *New England J. Med.*, 202: 1252, 1930.
36. Schuster, X. Cited in reference 35.
37. Willius, F. A. Ventricular fibrillation in man with temporary cardiac recovery. *J. Lab. & Clin. Invest.*, 8: 518, 1923.
38. Pedrazzini, A. and Riniker, P. Isolierte metastatische Entzündung des Tawara-Knotens. *Schweiz. med. Wchnschr.*, 86: 152, 1956.
39. Jahn, H.-J. Die Fokaltoxikose in der Pathogenese des Adams-Stokesschen Syndroms. *Ztschr. f. Kreislaufforsch.*, 43: 354, 1954.
40. Wilson, F. N. and Robinson, G. C. Heart-block. II. Transient complete heart-block with numerous Stokes-Adams attacks. *Arch. Int. Med.*, 21: 181, 1918.
41. Luce, H. Zur Klinik und pathologischen Anatomie des Adams-Stokes'schen Symptomencomplexes. *Deutsches Arch. klin. Med.*, 74: 370, 1900.
42. Reuling, J. R. and Razinsky, L. Metastatic bronchiogenic carcinoma of the heart. *Am. Heart J.*, 21: 470, 1941.
43. Longcope, W. F. and Freiman, D. G. A study of sarcoidosis. Based on combined investigation of 160 cases including 30 autopsies from the Johns Hopkins Hospital and Massachusetts General Hospital. *Medicine*, 31: 1, 1952.
44. Gottfarb, G. and Wahlgren, F. Adams-Stokes syndrom framkallat av morbus Besnier-Boeck-Schaumann (sarcoidosis). *Nord. med.*, 52: 985, 1954.
45. Moberg, A. and Tillgren, C. Hjärtarytmi vid lymfogranulomatosis benigna (Schaumanns sjukdom). *Opuscula Medica*, 3: 197, 1958.
46. Botti, R. E. and Young, F. E. Myocardial sarcoid, complete heart block and aortic stenosis. *Ann. Int. Med.*, 51: 811, 1959.
47. Schmoll, E. Zwei Fälle von Adams-Stokes'scher Krankheit mit Dissoziation von Vorhof- und Kammerrhythmus und Läsion des His'schen Bündels. *Deutsches Arch. Klin. Med.*, 87: 554, 1906.
48. Wiltshire, H. A case of heart block illustrating the behaviour of the auricle during periods of prolonged ventricular silence. *Heart*, 10: 201, 1923.
49. Grassberger, A. Klinische, elektrokardiographische und histologische Untersuchung eines Falles von Adams-Stokesscher Erkrankung. *Ztschr. klin. Med.*, 112: 388, 1929.
50. Yater, W. M. and Willius, F. A. Heart block showing multiple transitions associated with convulsive syncope: report of a case with detailed histopathological study. *Am. Heart J.*, 4: 280, 1929.
51. Jagic, N. Ein Beitrag zur Kasuistik des Adams-Stokesschen Symptomenkomplexes. *Ztschr. klin. Med.*, 66: 183, 1908.
52. Major, R. H. Cited in reference 148.
53. Day, J. and Viar, W. N. A case of heart block treated with 1-cyclohexyl-2-methylaminopropane (benzedrex). *Am. Heart J.*, 42: 733, 1951.
54. Kornel, L. A case of calcified ventricular aneurysm with progressive heart block. *Cardiologia*, 32: 101, 1958.
55. Rawkins, M. D. and Konstarn, G. L. S. Complete heart-block associated with amoebic hepatitis. *Lancet*, 2: 152, 1949.
56. Legros, J. and Nassheuer, R. Syndrome d'Adams-Stokes aprés une coqueluche chez une enfant de 12 ans. Etude électrocardiographique. *Acta paediat. belg.*, 3: 238, 1949.
57. Shou-Chi, T'Ao. Paroxysmal ventricular fibrillation producing Adams-Stokes syndrome. Report of a case on quinidine therapy with spontaneous recovery. *Chinese M. J.*, 72: 342, 1954.
58. Binder, M. J. and Rosove, L. Paroxysmal ventricular tachycardia and fibrillation due to quinidine. *Am. J. Med.*, 12: 491, 1952.
59. Kerr, W. J. and Bender, W. L. Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart-block while under quinidine sulphate therapy. *Heart*, 9: 269, 1921.
60. Berthoud, E., Mercier, H. and Solms, H. Syndrome de Stokes-Adams par intoxication à la prostigmine. *Rev. méd. Suisse Rom.*, 73: 392, 1953.
61. Ceranke, P. and St. Tomek. Pilocarpinintoxikation bei Herzblock. *Wien. med. Wchnschr.*, 103: 131, 1953.
62. Fongi, E. G. and Burucuá, J. E. Bloqueo sinoauricular con sindrome de Morgagni-Stokes-Adams provocado per la estreptomicina. *Prensa méd. argent.*, 39: 1507, 1952.
63. T'Ao Shou-Chi. Cardiac manifestations of the toxic action of potassium antimony tartrate in schistosomiasis patients. Paroxysmal tachycardia and fibrillation. *Chinese M. J.*, 75: 365, 1957.
64. Avramidis, A. V. and Hsu, I. Digitalis-induced ventricular fibrillation. *Arch. Int. Med.*, 104: 277, 1959.
65. McGuire, J. and Richards, C. E. Fatal digitalis poisoning occurring in a normal individual. *Am. Heart J.*, 12: 109, 1936.
66. Nagayo, M. Pathologisch-anatomische Beiträge zum Adams-Stokesschen Symptomenkomplex. *Ztschr. klin. Med.*, 67: 495, 1909.
67. Wenckebach, K. F. and Winterberg, K. Die unregelmässige Herztätigkeit, p. 390. Leipzig, 1927. Engelmann, W.
68. Johansson, B. W. Adams-Stokes attacks precipitated by swallowing in a patient with bronchial carcinoma. *Am. J. Cardiol.*, 7: 874, 1961.
69. Renon, L., Géraudel, E. and Thibaut, D. Syndrome d'Adams-Stokes mortel sans lesion anatomique du coeur ni du système nervaux. *Bull. et mém. Soc. med. hôsp. Paris*, 35: 56, 1913.
70. Storstein, O. Adams-Stokes attacks caused by ventricular fibrillation in a man with otherwise normal heart. *Acta med. Scandinav.*, 133: 437, 1949.
71. Giraud, P., Erlande, G. and Bernard, R. Trouble du rythme cardiaque avec accidents convulsifs au cours d'un rheumatisme cardiaque. *Marseille-méd.*, 75: 591, 1938.
72. v. Kiss, P. Elektrokardiogramm des während

Diphterie auftretenden Adams-Stokesschen Anfalles. *Ztschr. ges. exper. Med.*, 93: 619, 1934.
73. Moltke, E. Adams-Stokes syndrome following acute hemorrhage in an eight year old girl. *Acta paediat.*, 44: 73, 1955.
74. Selander, P. Personal communication.
75. Bellet, S., de Leon, A. C. and Muller, O. F. Sensitivity of the ventricular pacemaker in complete A-V heart block to acidosis and hyperkalemia. Clinical and experimental study. *Circulation*, 20: 668, 1959.
76. Flaum, E. and Klima, R. Ein neurogen ausgelöster Fall von Adams-Stokes. *Klin. Wchnschr.*, 11: 1192, 1932.
77. Medvei, C. V. and Uiberall, H. Ueber schwere, von der Mund- und Pharynxschleimhaut auslösbare Rhythmusstörungen des Herzens. *Wien. klin. Wchnschr.*, 51: 234, 1938.
78. Johansson, B. W. A case of Adams-Stokes attacks disappearing after cholecystectomy. *Acta med. Scandinav.*, 168: 219, 1960.
79. Hofmann, H. Rhythmologische Untersuchungen zur Pathogenese Adams-Stokesscher Anfälle bei av-Block. *Ztschr. f. Kreislaufforsch.*, 44: 757, 1955.
80. Bockel, P. Morgagni-Adams-Stokes-Symptomenkomplex bei Herzblock mit abnorm langsamer Frequenz. *Ärztl. Wchnschr.*, 9: 785, 1954.
81. Winter, K.-A. Ein Beitrag zur Therapie des Kammerflimmerns. *Deutsche Gesundheitswesen*, 7: 980, 1952.
82. Wedd, A. M., Springs, C. and Wilson, D. C. Standstill of the heart of vagal origin. *Am. Heart J.*, 5: 493, 1930.
83. v. Hoesslin, H. Kammerwühlen und Adams-Stokesscher Symptomenkomplex. *Klin. Wchnschr.*, 4: 62, 1925
84. Broser, F. and Stühler, R. Zur Kasuistik der neurogenen Form Adams-Stokesscher Anfälle (ein Morgagni-Adams-Stokesscher Anfall in EEG und EKG). *Nervenarzt*, 26: 117, 1955.
85. Schnur, S. Newer concepts of Stokes-Adams syndrome. *Am. Heart J.*, 35: 298, 1948.
86. Fishberg, A. M. Heart Failure, p. 269. Philadelphia, 1937. Lea & Febiger.
87. Krüskemper, C. Ein kasuistischer Beitrag zur neurogenen Form des Adams-Stokes'schen Symptomen-Komplexes. *Zbl. f. Herz- und Gefässkrankheit*, 17: 117, 1925.
88. Gastaut, H. and Fischer-Williams, M. Electroencephalographic study of syncope. Its differentiation from epilepsy. *Lancet*, 2: 1018, 1957.
89. Bellville, J. W., Artusio, J. F. and Glenn, F. The electroencephalogram in cardiac arrest. *J.A.M.A.*, 157: 508, 1955.
90. Holzmann, M. Klinische Elektrokardiographie, p. 553. Zürich, 1945. Fretz and Wasmuth Verlag AG.
91. Sonne, C. Tilfaelde of sinusblok. *Ugesk. Laeg.* 93: 508, 1931.
92. Cowan, J. Some disturbances of the rhythm of the heart. *Brit. Heart J.*, 1: 3, 1939.
93. Schild, W. and Weise, H. Beitrag zur Therapie des sinu-auriculären Blocks. *Klin. Wchnschr.*, 30: 419, 1952.
94. Teichmann, G. Morgagni-Adams-Stokesscher Symptomenkomplex und Herzstillstand *Das deutsch. Gesundheitswesen*, 10: 103, 1955.
95. Tuna, N. and Scott, J. W. Stokes-Adams attacks with simultaneous auricular and ventricular standstill. *Circulation*, 9: 853, 1954.
96. Géraudel, E. Syndrome paroxystique d'Adams-Stokes par bradyarythmie sinusale. *Arch. mal. coeur*, 24: 288, 1931.
97. Christensen, A. M. and Dalgaard, F. Et tilfaelde av Adams-Stokes' syndrom. *Nord. med.*, 2: 1733, 1939.
98. Carter, E. P. and Dieuaide, F. R. Recurrent complete heart block with normal conduction between attacks. *Bull. Johns Hopkins Hosp.*, 34: 401, 1923.
99. Doane, J. C. and Krasnoff, S. O. Extreme bradycardia. *Am. Heart J.*, 36: 777, 1948.
100. Barnes, A. R. Cerebral manifestations of paroxysmal tachycardia. *Am. J. M. Sc.*, 171: 489, 1926.
101. Dock, W. Transitory ventricular fibrillation as a cause of syncope and its prevention by quinidine sulphate. *Am. Heart J.*, 4: 709, 1929.
102. Gallavardin, L. and Veil, P. Extra-systolie ventriculaire avec salves tachycardiques et accidents vertigineux. *Arch. mal. coeur*, 22: 25, 1929.
103. Levine, S. and Harvey, W. P. Clinical Auscultation of the Heart, p. 115. London, 1950. W. B. Saunders Co.
104. Groedel, F. M. and Kisch, B. Morgagni-Adams-Stokes: what does it represent? *Cardiologia*, 6: 43, 1942.
105. de Boer, S. Das Stokes-Adamssche Syndrom. *Cardiologia*, 1: 253, 1937.
106. Gonin, A., Gallavardin, L., Froment, R. and Cheynel. Apropos de 3 cas de syncope de "Morgagni-Adams-Stokes" par fibrillation ventriculaire. *Arch. mal. coeur*, 44: 398, 1951.
107. Robinson, G. C. and Bredeck, J. F. Ventricular fibrillation in man with cardiac recovery. *Arch. Int. Med.*, 20: 725, 1917.
108. Davies, D. and Sprague, H. B. Ventricular fibrillation: its relation to heart-block. *Am. Heart J.*, 4: 559, 1929.
109. Moe, T. Morgagni-Adams-Stokes attacks caused by recurrent ventricular fibrillation in a patient without apparent organic heart disease. *Am. Heart J.*, 37: 811, 1949.
110. Scott, R. W. and Sancetta, S. M. Stokes-Adams attacks induced by rectal stimulation in a patient with complete heart block. *Circulation*, 2: 886, 1950.
111. Lian, C. and Deparis, M. Deux syncopes avec fibrillation ventriculaire transitoire dans un pouls lent permanent par dissociation auriculo-ventriculaire complète. *Bull. soc. méd. hôp., Paris*, 50: 569, 1934.
112. Bjerlöv, H. A case of ventricular fibrillation recovered. *Acta med. Scandinav.* (suppl.), 50: 121, 1932.
113. Schwartz, S. P. and Jezer, A. The action of adrenalin on patients with complete heart-block and Stokes-Adams seizures. *Am. Heart J.*, 7: 652, 1932.
114. Schwartz, S. P. Transient ventricular fibrillation. A study of the electrocardiograms ob-

tained from a patient with auriculoventricular dissociation and recurrent syncopal attacks. *Arch. Int. Med.*, 49: 282, 1932.

115. Schwartz, S. P. and Hauswirth, L. Studies on transient ventricular fibrillation. II. Observations on the alterations in the rhythm of the heart preceding syncopal seizures in a woman with transient auriculoventricular dissociation. *Am. J. M. Sc.*, 187: 478, 1934.
116. Schwartz, S. P., Orloff, J. and Fox, C. Transient ventricular fibrillation. I. The prefibrillary period during established auriculoventricular dissociation with a note on the phonocardiograms obtained at such times. *Am. Heart J.*, 37: 21, 1949.
117. Robbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S. Adams-Stokes syndrome. The treatment of ventricular asystole, ventricular tachycardia and ventricular fibrillation associated with complete heart block. *Am. J. Med.*, 18: 577, 1955.
118. Levine, S. A. and Matton, M. Observations on a case of Adams-Stokes syndrome, showing ventricular fibrillation and asystole lasting five minutes with recovery following the intracardiac injection of adrenalin. *Heart*, 12: 271, 1926.
119. Parsonnet, A. E., Bernstein, A. and Klosk, E. Ventricular fibrillation. With special reference to the Morgagni-Adams-Stokes syndrome; report of an unusual case. *Am. Heart J.*, 31: 769, 1946.
120. Pastor, B. H. and Worrilow, S. H. Electrocardiographic patterns in Stokes-Adams syndrome. *Ann. Int. Med.*, 34: 80, 1951.
121. v. Hoesslin, H. Der Herztod. Nach elektrokardiographischen Aufnahmen. *Ergebn. inn. Med. u. Kinderh.*, 39: 276, 1931.
122. Linko, E. Morgagni-Adams-Stokes in oireyhtymästä. *Duodecim*, 70: 11, 1954.
123. v. Hoesslin, H. and Klapp, R. Vagusresektion bei Adams-Stokesschem Symptomenkomplex. *Klin. Wchnschr.*, 3: 1211, 1924.
124. Weiss, S. and Ferris, E. B., Jr. Adams-Stokes syndrome with transient complete heart block of vagovagal reflex origin. *Arch. Int. Med.*, 54: 931, 1934.
125. Gluch, B. Elektrokardiographische Beobachtungen bei dem Morgagni-Adams-Stokes'schen Symptomen-Komplex. *Ztschr. Kreislaufforsch.*, 24: 561, 1932.
126. Dressler, W. Permanenter Knotenrhythmus mit Anfällen von Bewusstlosigkeit verursacht durch Kammerflattern. *Klin. Wchnschr.*, 8: 165, 1929.
127. Zwillinger, L. Ueber die Magnesiumwirkung auf das Herz. *Klin. Wchnschr.*, 14: 1429, 1935.
128. Gresham, G. A. A case of ventricular fibrillation. *Brit. Heart J.*, 14: 527, 1952.
129. Dupler, D. Ventricular arrhythmia and Stokes-Adams syndrome. Report of a case. *Circulation*, 7: 585, 1953.
130. Schmidt, W. Elektrokardiographische Beobachtungen bei Morgagni-Adams-Stokesschen Anfällen. *Ärztl. Forsch.*, 9: 519, 1955.
131. Stokes, W. Paroxysmal heart block in bundle branch block. *Brit. Heart J.*, 9: 267, 1947.
132. Bourne, G. Stokes-Adams attacks in bundle-branch block. *Brit. Med. J.*, 2: 1311, 1955.
133. Cookson, H. Paroxysmal ventricular standstill. *Brit. Heart J.*, 14: 350, 1952.
134. Söderström, N. The diagnosis of partial atrioventricular block and Adams-Stokes syndrome in patients with auricular fibrillation. *Cardiologia*, 33: 397, 1958.
135. Thomsen, V. Et tilfaelde af sinusarythmi med optraeden af Stokes-Adams syndrom. *Ugesk. Laeger*, 96: 426, 1934.
136. Schild, W. and Weise, H. Beitrag zur Therapie des Sinu-auriculären Blocks. *Klin. Wchnschr.*, 30: 419, 1952.
137. Volhard, F. Ueber die Beziehungen des Adams-Stokes'schen Symptomenkomplexes zum Herzblock. *Deutsches Arch. klin. Med.*, 97: 348, 1909.
138. White, P. D. Un cas de dissociation auriculoventriculaire complète avec reductions transitoires à moitié de la fréquence ventriculaire. *Arch. mal. coeur*, 11: 532, 1918.
139. Hick, F. K. Stokes-Adams seizures. Case report of "paroxysmal ventricular standstill" and its production by carotid sinus pressure. *Circulation*, 9: 857, 1954.
140. Johansson, B. and Vendsalu, A. The influence of adrenaline, noradrenaline, and acetylcholine on the electrocardiogram of the isolated perfused guinea-pig heart. *Acta physiol. Scandinav.*, 39: 356, 1957.
141. Erlanger, J. On the physiology of heart-block in mammals, with especial reference to the causation of Stokes-Adams disease. *J. Exper. Med.*, 7: 676, 1905.
142. Bäumler, C. Vollständiger Herzstillstand, anfallsweise in Cheyne-Stokesschen Atmen bei einem jugendlichen Herzkranken auftretend. *Zbl. Herzkrankh.*, 4: 1, 1912.
143. Griffith, T. W. A clinical study of three cases of heart-block. *Brit. Med. J.*, 1: 763, 1921.
144. Beck, C. S. Coronary heart disease after twenty-five years. *J. Thoracic Surg.*, 36: 329, 1958.
145. Zoll, P. M., Linenthal, A. J., Gibson, W., Paul, M. M. and Norman, L. R. Intravenous drug therapy of Stokes-Adams disease. Effects of sympathomimetic amines on ventricular rhythmicity and atrioventricular conduction. *Circulation*, 17: 325, 1958.
146. Chandler, D. and Clapper, M. I. Complete atrioventricular block treated with isoproterenol hydrochloride. *Am. J. Cardiol.*, 3: 336, 1959.
147. Kjellin, K., Müller, R. and Widén, L. Glossopharyngeal neuralgia associated with cardiac arrest and hypersecretion from the ipsilateral parotid gland. *Neurology*, 9: 527, 1959.
148. Bellet, S. The treatment of Stokes-Adams seizures. *Mod. Concepts Cardiovas. Dis.*, 26: 393, 1957.
149. Dragsted, P. J. and Møller, P. F. Behandling av Adams-Stokes' anfald med natriumlactat. *Ugesk. Laeger*, 120: 1458, 1958.
150. Cohn, A. E. and Levine, S. A. The beneficial effects of barium chloride on Adams-Stokes disease. *Arch. Int. Med.*, 36: 1, 1925.
151. Strauss, S. and Meyer, J. The treatment of transient ventricular standstill with barium chloride. *Am. Heart J.*, 3: 328, 1928.
152. Levine, S. A. Clinical Heart Disease, p. 207, 3rd edition. London, 1946. W. B. Saunders Co.

153. McMillan, T. M. and Wolferth, C. C. An untoward effect of barium chloride in producing short runs of aberrant ventricular beats. *J. Lab. & Clin. Med.*, 14: 839, 1929.
154. Scherf, D. Der Morgagni-Adams-Stokes-Symptomenkomplex und seine Behandlung. *Wien. klin. Wchnschr.*, 49: 83, 1936.
155. Hörmann, J. Zur Therapie des Adams-Stokesschen Syndroms. *Deutsch. Med. Wchnschr.*, 77: 1026, 1952.
156. Parade, G. W. and Voit, K. Zur Adrenalin- und Ephetoninbehandlung der Adams-Stokesschen Krankheit. *Deutsch med. Wchnschr.*, 55: 179, 1929.
157. Böres, W. Ein Beitrag zur Behandlung des totalen atrioventrikulären Herzblocks. *Med. Monatschr.*, 4: 120, 1950.
158. Diamond, S. and Flaxman, N. The use of methamphetamine hydrochloride in Stokes-Adams disease. *Am. Pract. & Digest. Treat.*, 6: 1174, 1955.
159. Sigler, L. H. Treatment of the Stokes-Adams syndrome by hypertonic glucose solution given intravenously. *Ann. Int. Med.*, 13: 101, 1939.
160. Callaghan, J. C. and Bigelow, W. G. An electrical artificial pacemaker for standstill of the heart. *Ann. Surg.*, 134: 8, 1951.
161. Zoll, P. Resuscitation of the heart in ventricular standstill by external stimulation. *New England J. Med.*, 247: 768, 1952.
162. Zoll, P. M., Linenthal, A. J. and Norman, L. R. Treatment of Stokes-Adams disease by external electric stimulation of the heart. *Circulation*, 9: 482, 1954.
163. Dittmar, A., Friese, G. and Nusser, E. Ueber die Behandlung des Kammerstillständes beim Morgagni-Adams-Stokesschen Symptomenkomplex mit einem elektrischen Schrittmacher. *Ztschr. Kreislaufforsch.*, 45: 416, 1956.
164. Kaye, M., Schickler, O., Rosenfeld, I. and Lapin, A. Successful treatment of ventricular arrest during complete heart block by external electrical stimulation. *Am. Heart J.*, 51: 460, 1956.
165. Rosenfeld, I. and Segall, H. N. An external cardiac pacemaker in the treatment of Stokes-Adams syndrome: report of three cases. *Am. Heart J.*, 50: 749, 1955.
166. Furman, S. and Schwedel, J. B. An intracardiac pacemaker for Stokes-Adams seizures. *New England J. Med.*, 261: 943, 1959.
167. Jackson, A., Youmans, R., McCaughey, H., Pickard, C. M. and Faw, M. The cardiac pacemaker. Its use for more than seven months in one patient. *J. Kansas Med. Soc.*, 58: 735, 1957.
168. Elmquist, R. Personal communication.
169. Landegren, J. Personal communication.
170. Chapman, R. A. Use of quinidine sulfate and of procaine amide in a patient with paroxysmal ventricular tachycardia. *Arch. Int. Med.*, 90: 90, 1952.
171. Schwartz, S. P., Hallinger, L. and Imperialli, A. Transient ventricular fibrillation. IV. The effects of procaine amide on patients with transient ventricular fibrillation during established auriculo-ventricular dissociation. *Circulation*, 6: 193, 1959.
172. Zoll, P. M., Linenthal, A. J. and Zarsky, L. R. N. Ventricular fibrillation. Treatment and prevention by external electric currents. *New England J. Med.*, 262: 105, 1960.
173. Zoll, P. M., Linenthal, A. J., Reider, R. B., Gibson, W. and Norman, L. R. Treatment and prevention of ventricular fibrillation in Stokes-Adams disease. *Circulation*, 18: 803, 1958.
174. Conklin, W. H., Beebe, R. T. and Frawley, T. F. Ventricular fibrillation due to myocardial infarction with survival. *Arch. Int. Med.*, 104: 281, 1959.
175. Prinzmetal, M. and Kennamer, R. Emergency treatment of cardiac arrhythmias. *J.A.M.A.*, 154: 1049, 1954.
176. Friedberg, C. K., Kahn, M., Scheuer, J., Bleifer, S. and Dack, S. Adams-Stokes syndrome associated with chronic heart block. Treatment with corticosteroids. *J.A.M.A.*, 172: 1146, 1960.
177. McLemore, G. A., Jr. and Levine, S. A. The possible therapeutic value of cholecystectomy in Adams-Stokes disease. *Am. J. M. Sc.*, 229: 386, 1955.
178. Ray, B. S. and Stewart, H. J. Glossopharyngeal neuralgia: a cause of cardiac arrest. *Am. Heart J.*, 35: 458, 1948.
179. Richburg, P. L. and Kern, C. E. Glossopharyngeal neuralgia with syncope and convulsions. *J.A.M.A.*, 152: 703, 1953.
180. Laslett, E. E. Syncopal attacks, associated with prolonged arrest of the whole heart. *Quart. J. Med.*, 2: 347, 1908–09.
181. Andersen, M. S. A case of sino-auricular heart block with Stokes-Adams attacks. *Acta med. Scandinav.*, 78: 216, 1932.

Case Reports

Primary Pulmonary Hypertension

Effect of Unilateral Pulmonary Artery Occlusion and Infusion of Acetylcholine*

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INCREASED PULMONARY vascular tone has been suggested as an important factor in the etiology and pathogenesis of primary pulmonary hypertension and the ensuing right ventricular hypertrophy and failure.[1–4] Pathologic changes observed are all compatible with pulmonary hypertension due to any cause.[5] All attempts at treatment with hypotensive drugs or by surgical means have failed to alter the inexorable course of the disease.[2,3,5,6] A method for lowering the high pulmonary vascular resistance present, similar to that used in systemic hypertension, would be obviously desirable if the pulmonary blood vessels were still reactive.

Utilizing the method of temporary unilateral pulmonary arterial occlusion in patients with pulmonary hypertension due to mitral stenosis or cardiac failure,[7] or chronic pulmonary disease,[8] a marked decrease in arteriolar resistance was observed in the unoccluded lung. In these studies sudden release of tone was produced despite very high initial resistances.

Recently, acetylcholine has been shown to lower pulmonary artery pressure when injected directly into the pulmonary artery at a dosage level which would not affect systemic pressure.[9] When infused at a suitable constant rate into the pulmonary artery, a decrease in pressure and vascular resistance occurs in normal subjects and this reduction is accentuated when the pulmonary artery pressures are raised by hypoxia.[10,11] In patients with pulmonary hypertension secondary to mitral valvular disease the effect is even more striking.[12–14] Wood et al.[12] also noted a marked reduction of pressure in patients with primary pulmonary hypertension.

It is the purpose of this communication to report the results of temporary unilateral pulmonary artery occlusion and infusion of acetylcholine in a patient with primary pulmonary hypertension proved by cardiac catheterization and pulmonary biopsy.

CASE HISTORY

This twenty-nine year old Negro woman was admitted to the hospital with a two week history of progressive swelling of the abdomen and edema of the face and extremities, weakness and faintness on effort. Slight systemic hypertension had been noted during pregnancy two years prior to admission.

On physical examination, the arterial blood pressure was 160/110 mm. Hg, the pulse was 96 per minute and regular, respirations 16 per minute and temperature 98.8°F. The significant findings included edema of the face, liver edge palpable 3 fingerbreadths below the right costal margin, signs of abdominal fluid and 3 plus pitting edema of the extremities. A soft diastolic murmur was heard to the left of the sternum in the third and fourth intercostal spaces and, at times, a systolic murmur was also audible. The pulmonic second sound was tambouric and split. The lungs were clear.

Roentgenogram of the chest and an electrocardiogram showed right ventricular hypertrophy (Figs. 1 and 2). Results of ventilatory function studies were within normal limits.

She was treated with digitalis and mercurial diuret-

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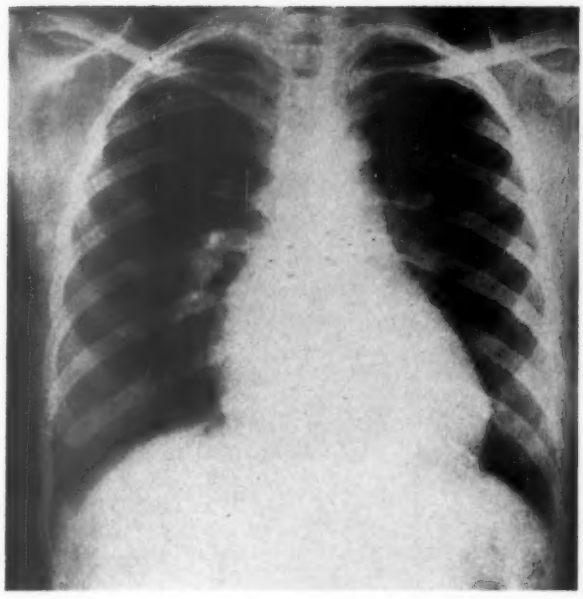


FIG. 1. Chest roentgenogram.

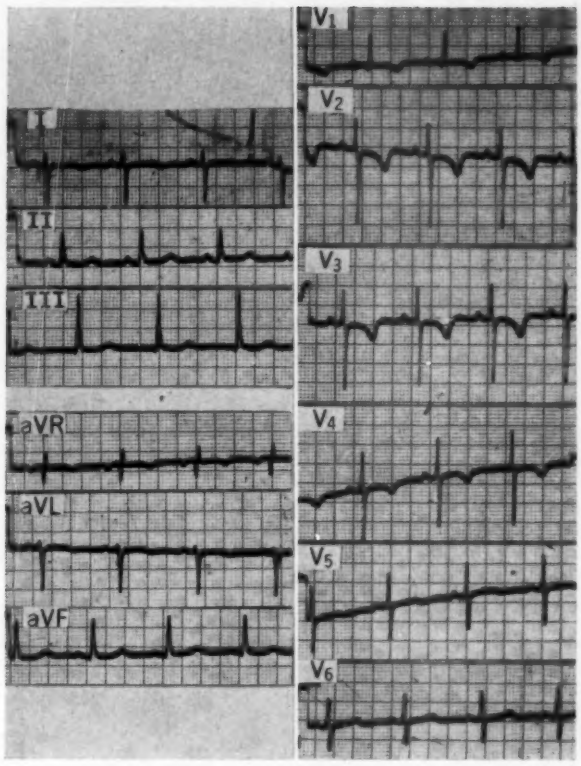


FIG. 2. Routine electrocardiogram.

ics and showed an excellent response with a fourteen pound weight loss. *Lung biopsy* revealed some evidence of pulmonary vascular disease (Fig. 3) but most sections were normal.

METHODS

Cardiac catheterization was carried out in a resting postabsorptive state. Pulmonary function studies had been performed on the previous day to acquaint the patient with laboratory surroundings and personnel. No premedication was given. A special triple lumen catheter was used with an inflatable cuff on the middle lumen as previously described.[15] The catheter was positioned fluoroscopically in the right main pulmonary artery so that the proximal lumen lay just beyond the pulmonic valve and the cuff just at the root of the right main pulmonary artery. An indwelling arterial needle was placed in the brachial artery for measurements of pressure and sampling of arterial blood. A polyethylene tube with lead sinker was placed fluoroscopically in the esophagus at the level of the seventh thoracic vertebra for measurement of esophageal (i.e., intrapleural) pressures.[16]

After resting twenty minutes control values were obtained. Pulmonary wedge pressure could not be obtained. Pulmonary arterial pressure was obtained by a Sanborn electromanometer and brachial and esophageal pressures measured via Statham strain gauges. Respiratory minute volumes were determined by collection of expired air in Douglas bags for ten minute periods and oxygen consumption and respiratory quotients determined by analysis on a Scholander 0.5 cc. gas analyzer. Blood samples were analyzed by the spectrophotometric method of Huckabee[17] and by Van Slyke manometric techniques.[18] Cardiac output was determined by Fick principle and pulmonary vascular resistance calculated from standard formulas. The wedge pressure was not obtained; therefore, the pressure distal to occlusion was used as pulmonary wedge pressure. This distal pressure has been identical with wedge pressures.[19]

After control values were obtained, the cuff in the right main pulmonary artery was inflated under fluoroscopic control with 35 per cent Diodrast.® However, the catheter was pulled distally and probably occluded only the right middle and lower lobes. No symptoms ensued and after fifteen minutes, repeat studies were obtained. The cuff was then deflated and, after the pressures were stabilized, an infusion of acetylcholine, 0.5 mg. per minute, into the main pulmonary artery was begun. After fifteen minutes of infusion repeat studies were again obtained.

RESULTS

The findings of cardiac catheterization are listed in Table I. Severe pulmonary hypertension and slight systemic hypertension were noted. The control cardiac output, arteriovenous oxygen difference and peripheral oxygen saturation were within normal limits. The

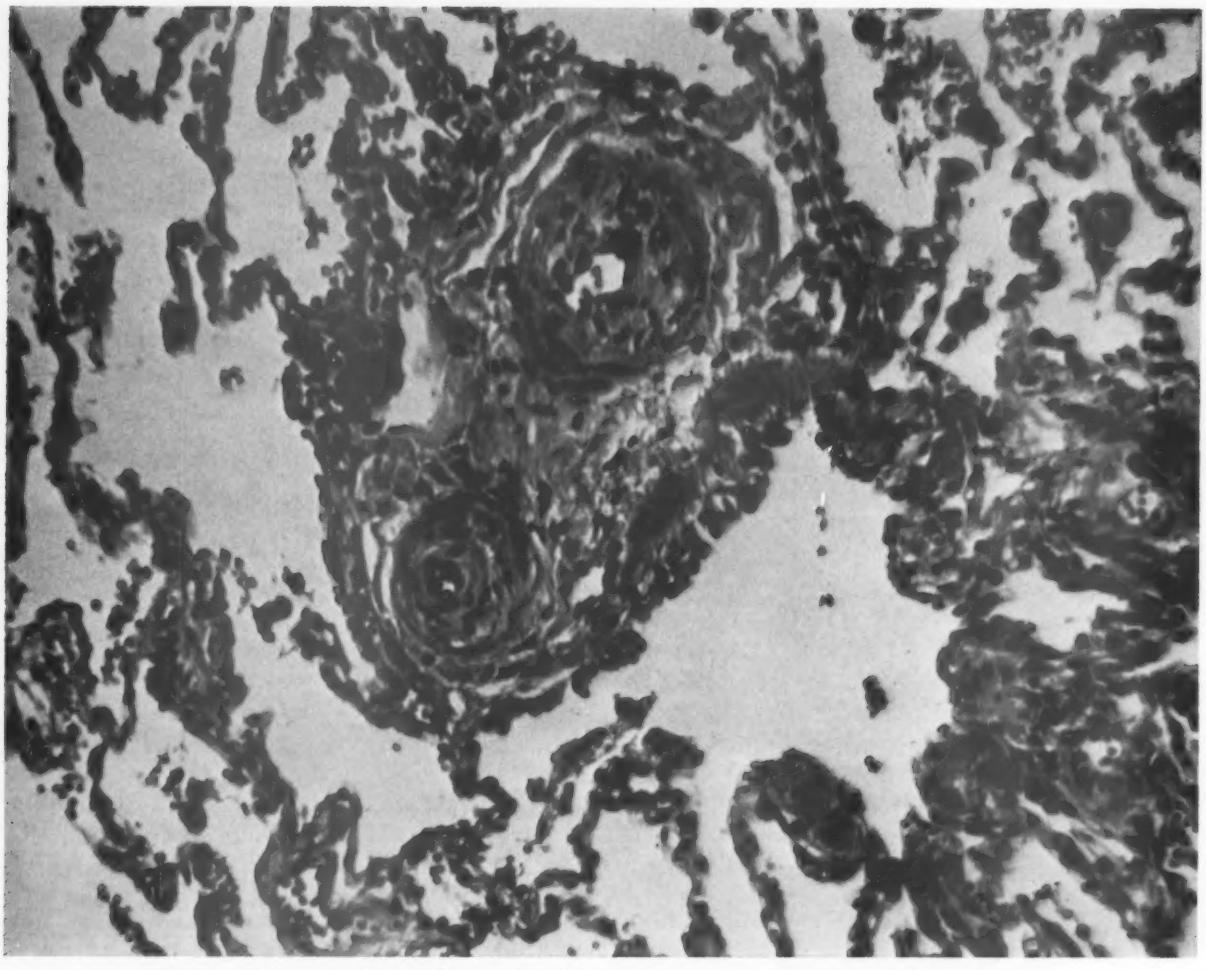


FIG. 3. Biopsy specimen of lung showing some degree of pulmonary arteriolar disease.

TABLE 1
Catheterization Findings

Effects	Pressures (mm. Hg)									Arterial Oxygen
	Pulmonary Artery				Brachial artery			Esophageal		Capacity (vol. %)
	S	D	M	Distal	S	D	M	Inspiration	Expiration	
Control	100	65	74	...	150	105	122	−5	0	15.6
Occlude right, middle and lower lobes	106	70	77	5	130	105	117	−5	−1	15.6
Acetylcholine infusion (0.5 mg./min.)	42	20	35	...	150	110	130	−3	0	15.6

NOTE: Right ventricular pressure, 100/5 (mean pressure, 48). S = systolic; D = diastolic; M = mean.

markedly elevated pulmonary arteriolar resistance is evident.

Following occlusion of the arteries to the right middle and lower lobes, a slight increment in main pulmonary arterial pressure occurred while the peripheral arterial pressure fell (Fig. 4A). No change was noted in esophageal pressure. The pressure beyond the occluding cuff fell to wedge levels as previously described. Peripheral oxygen saturation remained within normal limits. However, the arteriovenous difference increased and cardiac output fell slightly. Although the total calculated pulmonary arteriolar resistance apparently increased, the actual resistance of the perfused lung had decreased by at least one-third since the total perfusion of the lungs was now proceeding via the left lung and upper lobe of the right lung only.

With infusion of acetylcholine, a striking decrease was noted in pulmonary artery pressure and at the same time a sharp transient rise in systemic pressure with gradual return to control levels (Fig. 4B). Esophageal pressure and heart rate were unchanged and only a transient decrease in respiratory rate took place. Systemic arterial oxygen saturation fell and cardiac output rose. Marked decrease in pulmonary arteriolar resistance was evident. After cessation of the infusion, the pulmonary artery pressure returned to control levels within fifteen minutes.

Comments

As we have demonstrated previously, many patients with pulmonary hypertension due to cardiac or pulmonary disease can withstand occlusion of one main pulmonary artery without change in cardiac output or pulmonary artery pressure.[7,8] This was also true in this instance although some fall in cardiac output and systemic pressure did occur, indicating incomplete release of tone and fall in resistance of the perfused lung.

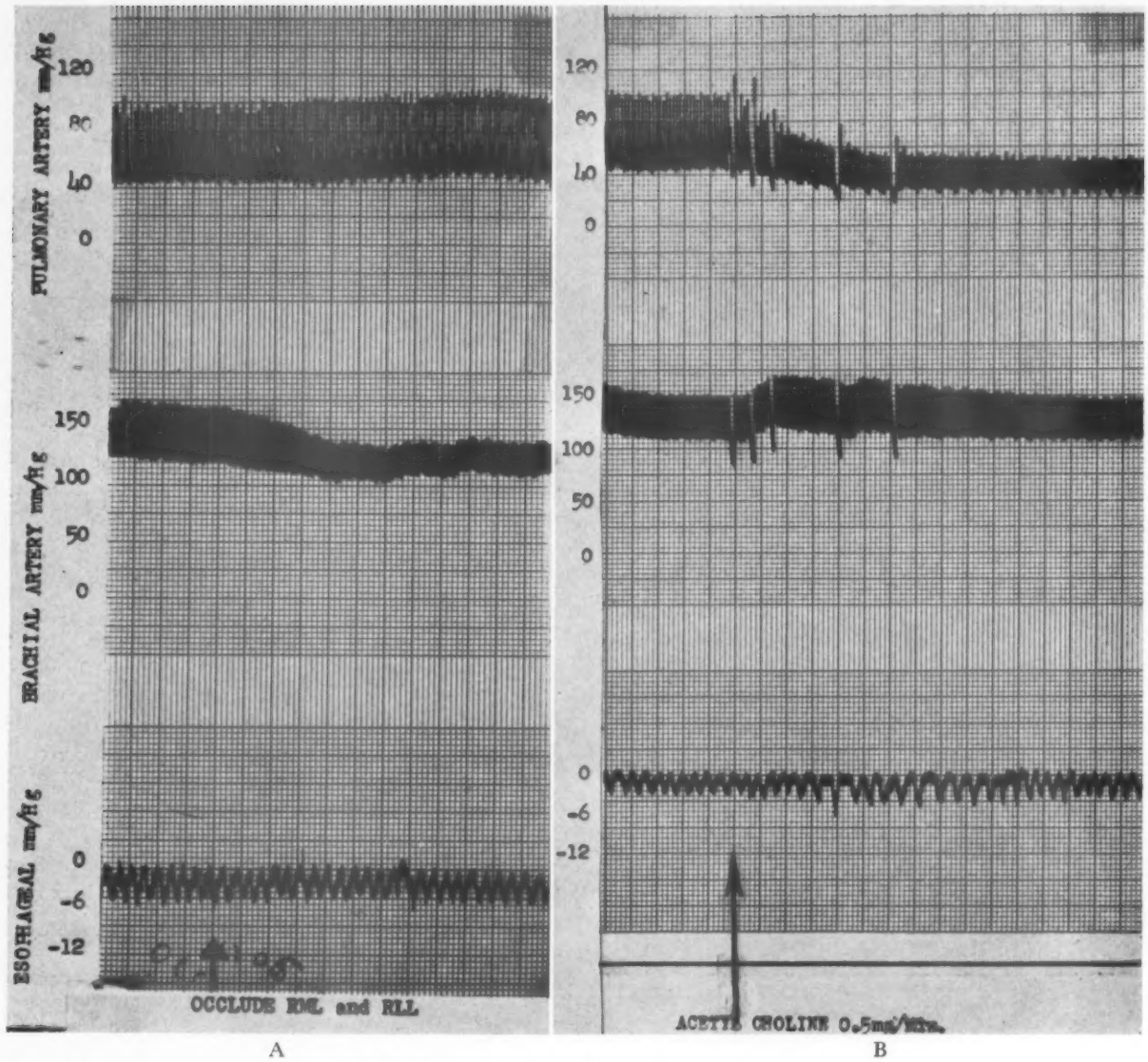
Infusion of acetylcholine evoked profound decrease in pulmonary arterial pressure and arteriolar resistance. The only change in systemic vascular pressure was a temporary increase due to the abrupt release of pulmonary arteriolar tone and the increased cardiac output. No change in heart rate or respiratory rate occurred, emphasizing the absence of systemic effect. The action of the drug seems to be directly on the pulmonary arterioles, as suggested by Wood et al.[12] and Soderholm and Werko.[13] The fall in arterial oxygen saturation was noted in the present study and coincides with other reports.[13] It seems likely that the augmented pulmonary blood flow and release of tone of vessels perfusing poorly ventilated alveoli resulted in venous admixture in the lung and systemic hypoxemia.

This patient is of particular interest because of the evidence of high degree of tone of the pulmonary vessels with very little demonstrable

Table 1 (*Continued*)

Arterial Oxygen		A-V O_2 Difference (vol. %)	O_2 Concentration (cc./min.)	Respiratory Minute Volume (L./min.)	Respiratory Quotient	Cardiac Output (L./min.)	Cardiac Index (L./min./M^2)	Pulmonary Arteriolar Resistance* (dynes sec. cm^{-5})
Content (vol. %)	Per Cent Saturation							
14.5	93	4.1	193	6.9	0.97	4.7	3.1	1153
14.5	93	5.1	226	8.1	0.94	4.4	2.9	1311
13.8	89	4.0	209	6.8	0.89	5.2	3.4	463

$$* R = \frac{PA_M - LA_M \times 1332 \times 60 \text{ sec.}}{CO \times 1000 \text{ cm.}^5}$$



A B

FIG. 4. A, effect of occlusion of right middle and lower lobe branches of pulmonary artery, on pulmonary artery, brachial artery and esophageal pressures. B, effect of infusion of acetylcholine, 0.5 mg. per minute, directly into main pulmonary artery on pulmonary artery, brachial artery and esophageal pressures.

histologic change. It is suggested that the increase in tone is the primary difficulty in this disease and that the pathologic changes are secondary to long-standing pulmonary vasospasm. The mechanism of the increased tone is as yet unexplained.

SUMMARY

A case of primary pulmonary hypertension is presented with evidence of increased vascular tone. Temporary unilateral occlusion of right middle and lower lobes caused a decrease in estimated arteriolar resistance of unoccluded lung. Infusion of acetylcholine caused a profound decrease in pulmonary artery pressure and pulmonary arteriolar resistance without any systemic effects, suggesting direct action of the drug on the pulmonary arterioles.

It is suggested that, in this case, increased tone is the primary defect and the histologic vascular changes secondary.

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REFERENCES

1. DRESDALE, D. T., MICHTOM, R. J. and SCHULTZ, M. Recent studies in primary pulmonary hypertension

including pharmacodynamic observations on pulmonary vascular resistance. *Bull. New York Acad. Med.*, 30: 195, 1954.

2. Dresdale, D. T., Schultz, M. and Michtom, R. J. Primary pulmonary hypertension. *Am. J. Med.*, 11: 686, 1951.
3. Wood, P. Diseases of the Heart and Circulation, p.836. London, 1956. Eyre & Spottiswood.
4. Shepherd, J. T., Edwards, J. E., Burchell, H. B., Swan, H. J. C. and Wood, E. H. Clinical, physiological and pathological considerations in patients with idiopathic pulmonary hypertension. *Brit. Heart J.*, 19: 70, 1957.
5. Whitaker, W. and Heath, O. Idiopathic pulmonary hypertension: etiology, pathogenesis, diagnosis and treatment. *Prog. Cardiovas. Dis.*, 1: 380, 1959.
6. Wade, G. and Ball, J. Unexplained pulmonary hypertension. *Quart J. Med.*, 26: 83, 1957.
7. Charms, B. L., Brofman, B. L. and Kohn, P. M. Pulmonary resistance in acquired heart disease. *Circulation*, 20: 5, 1959.
8. Charms, B. L., Brofman, B. L., Elder, J. C. and Kohn, P. M. Unilateral pulmonary artery occlusion in man. II. Studies in patients with chronic pulmonary disease. *J. Thoracic Surg.*, 35: 316, 1958.
9. Harris, P. Influence of acetylcholine on the pulmonary arterial pressure. *Brit. Heart J.*, 19: 272, 1957.
10. Fritts, H. W., Jr., Harris, P., Clauss, R. H., Odell, J. E. and Cournand A. The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. *J. Clin. Invest.*, 37: 99, 1958.
11. Fritts, H. W., Jr. and Cournand, A. Physiological factors regulating pressure flow and distribution of blood in the pulmonary circulation. In: Pulmonary Circulation, p. 62. Edited by Adams, W. and Veith, J. New York, 1959. Grune & Stratton.
12. Wood, P., Besterman, E. M., Towers, M. K. and McIlroy, M. B. The effect of acetylcholine on pulmonary vascular resistance and left atrial pressure in mitral stenosis. *Brit. Heart J.*, 19: 279, 1957.
13. Soderholm, B. and Werko, L. Acetylcholine and the pulmonary circulation in mitral valvular disease. *Brit. Heart J.*, 31: 1, 1959.
14. Marshall, R. The physiology and pharmacology of the pulmonary circulation. *Prog. Cardiovas. Dis.*, 1: 341, 1959.
15. Brofman, B. L., Charms, B. L., Kohn, P. M., Elder, J., Newman, R. and Rizika, M. Unilateral pulmonary artery occlusion in man. *J. Thoracic Surg.*, 34: 206, 1957.
16. Cherniack, R. M., Farhl, L. E., Armstrong, B. W. and Proctor, D. F. Comparison of esophageal and intrapleural pressure in man. *J. Appl. Physiol.*, 8: 203, 1955.
17. Huckabee, E. Spectrophotometric analysis of uncontaminated blood for oxyhemoglobin. *J. Lab. & Clin. Med.*, 46: 486, 1955.
18. Van Slyke, D. D. and Neill, J. M. Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
19. Charms, B. L., Brofman, B. L. and Adicoff, A. A. Factors affecting the pulmonary "capillary" pressure. *Am. J. Cardiol.*, 5: 328, 1960.

Organic and Functional Pulmonary Atresia with Intact Ventricular Septum*

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PULMONARY ATRESIA with intact ventricular septum (normal aortic root) has been recognized pathologically[1–6] since 1783. The clinical recognition, however, has not been possible until recent years.[7–10] According to Keith et al.[7] the condition is uncommon, occurring in less than 1 per cent of cases of congenital heart disease, and death in infancy is the rule.

The fundamental anomaly lies in the fused pulmonary valves which completely separate the right ventricular cavity from the pulmonary artery. As a rule the pulmonary valves appear as a diaphragm with three equidistant ridges radiating from the center to the wall of the pulmonary trunk. In the majority of cases[11] the right ventricular cavity is small with gross hypertrophy of the walls, the ventricular septum is, of course, intact and the tricuspid valves, although diminutive, are properly formed. A normally functioning tricuspid valve appears to be the key to this appearance; blood entering the right ventricle during diastole is trapped in the right ventricle during systole. Edwards[11] regards this mechanism as being responsible for the hypertrophy of the right ventricle, without producing dilatation. Brown[12] states that stenosis of the tricuspid valve is present frequently and Paul and Lev[10] make the point that some degree of tricuspid incompetence must be present to permit bidirectional movement of blood across the tricuspid valve, preventing the stasis and thrombosis which are known to occur otherwise.[13]

Greenwold et al.,[9] however, point out that there is a second group of cases in which the right ventricular cavity is large, hypertrophied and dilated. This probably depends on the presence of a considerable degree of incompetence of the tricuspid valve. The right ventricle can become dilated and hypertrophied if, during systole, blood can be expelled freely into the right atrium. Occasionally, in fact, cases have been described in which septal cusps of the tricuspid valve have been found adherent to the ventricular septum. An associated Ebstein's malformation has rarely been reported.[7]

A communication between the right and left atrium, usually a patent foramen ovale and, rarely, an atrial septal defect, is always present. The right atrium is hypertrophied and dilated and may, in fact, be aneurysmal. The circulation must flow entirely through the mitral valve into the left ventricle, which functions as a single ventricle with a single outlet, the aorta. The lungs receive their entire blood supply from the ductus arteriosus. The pulmonary trunk and branches, although reduced in size, are normally formed and the size of the ductus determines the vascular supply to the lungs. The circulatory pathway is thus from the right side of the heart to the left via the atrium and from the aorta to the lungs via the ductus.

It is the purpose of this report to describe three cases of organic pulmonary atresia with tricuspid incompetence and right ventricular enlargement. A fourth case is also described in which, although the pulmonary valves were normally formed with a normal pulmonary arterial orifice, functional pulmonary atresia was present.

CASE REPORTS

CASE 1. M. J., a female colored infant two months of age, was admitted with a respiratory infection.

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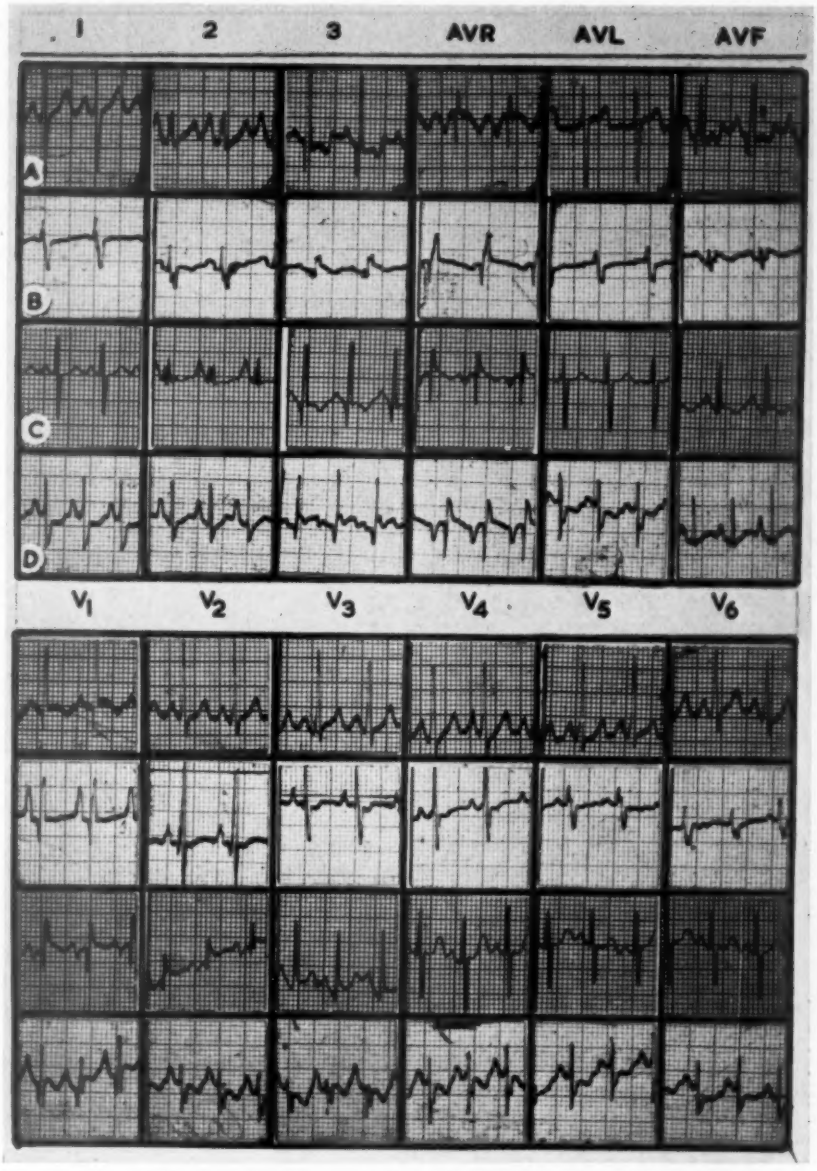

FIG. 1. Electrocardiograms of Cases 1 through 4 (A–D). See text.

One of eight children, she had been regarded as normal by her mother until the day before admission when she became irritable, cried and turned blue. She began to cough, breathed rapidly and vomited. Jerking movements of the hands appeared and her eyes rolled upwards.

On examination, the infant was cold and central and peripheral cyanosis was present. There were small purpuric spots on her right cheek. The pulses were all within normal limits and the liver was not distended. The heart, however, was considerably enlarged. A pansystolic murmur (grade 3/6) was audible over the whole of the front of the chest, being maximal in the fourth left and right parasternal spaces. Radiation to the lower right side of the chest was a feature. There was a loud triple rhythm; splitting of the second heart sound was not detected. The hemoglobin was 18.5 gm. per cent.

The electrocardiogram (Fig. 1A) showed right axis deviation (+120°) with a clockwise loop in the frontal plane. Marked right atrial enlargement was present with a P wave of 5 mm. in lead II. In lead V_1 there was a Q wave of 3 mm. and an R of 13 mm. The T wave was inverted. The intrinsicoid deflection was 0.03 second. A dominant R wave was still present in V_6.

The roentgenogram showed a tremendously enlarged cardiac shadow almost filling the whole of the chest (Fig. 2A). This shadow was due mainly to aneurysmal enlargement of the right atrium and enlargement

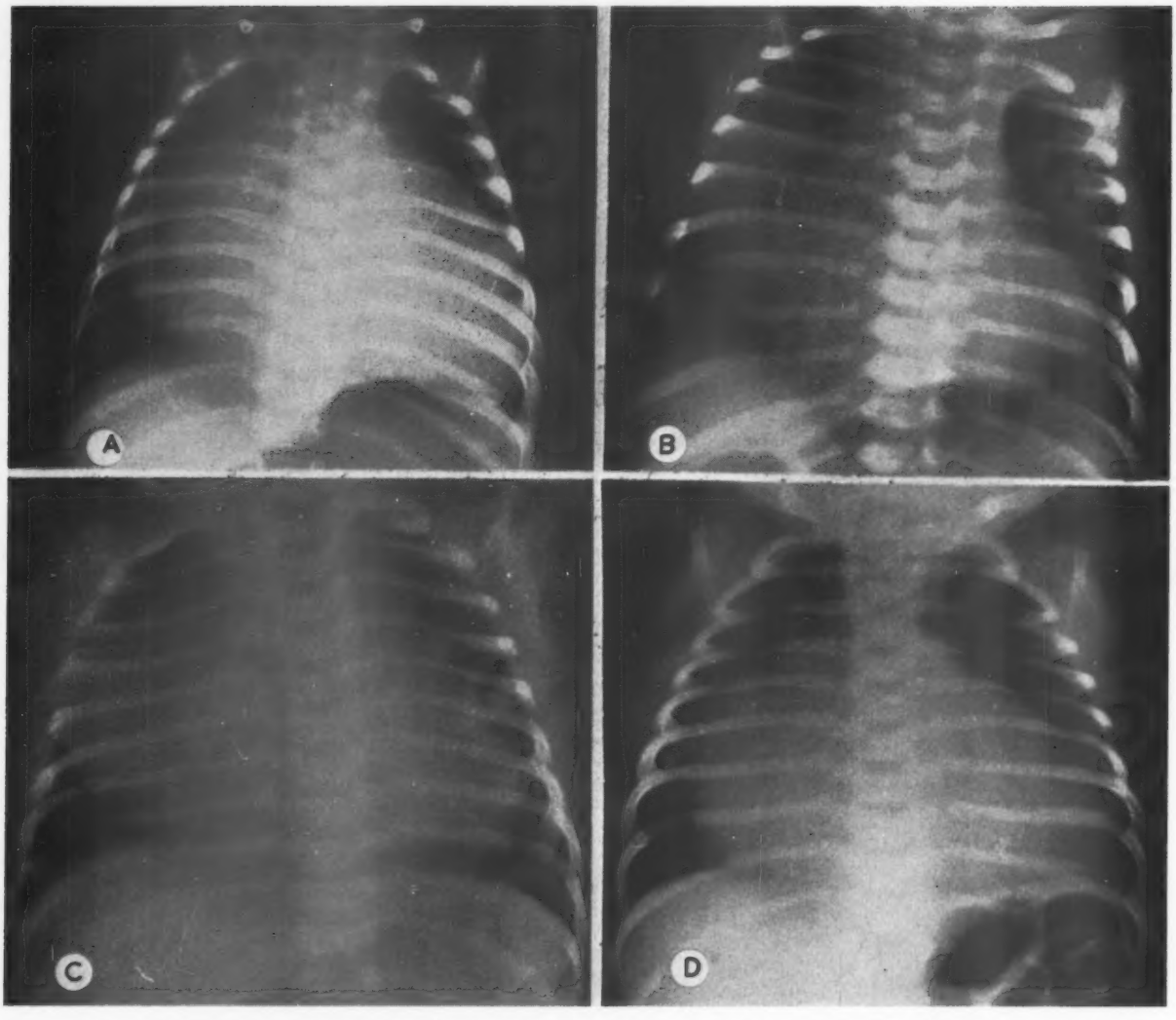

FIG. 2. A–P roentgenograms of Cases 1 through 4 (A–D). Note tremendous cardiomegaly in all four cases (cardiothoracic ratios 82–85) due mainly to aneurysmal right atrial enlargement. Pulmonary oligemia is present in every case.

of the right ventricle. Prominence of the pulmonary segment was noted. The lung fields that were visible appeared to be oligemic.

The baby was placed in an oxygen tent, digitalized and treated with broad spectrum antibiotics. Her condition deteriorated and she died eight days after admission.

At necropsy, the heart was grossly enlarged, mainly to the right, with compression of the right lung. The enlargement was chiefly due to aneurysmal dilatation of the right atrium and hypertrophy and dilatation of the right ventricle. There was no opening between the main pulmonary artery and the right ventricle, the obstruction being at the level of the valve which was absent (Fig. 3). The pulmonary arteries were narrower than normal. A large atrial septal defect was present. The ductus arteriosus was patent but very narrow with a circumference of only 0.8 cm. The chambers of the left side of the heart were apparently within normal limits, apart from slight left ventricular hypertrophy. The liver and spleen were congested and small bilateral pleural effusions were present.

CASE 2. S. H., a colored female infant four days old, was admitted to the Red Cross War Memorial Childrens' Hospital with a history of limpness, cyanosis and respiratory distress with periods of apnea of one day's duration.

On examination the child was very distressed, limp and generally cyanosed (grade 2/4). Edema of the feet was present. The pulse rate was 160 per minute, of normal volume, and the respiratory rate was 70 per minute with recession of the lower intercostal spaces. The abdomen was distended and the liver enlarged to 3 cm. below the costal margin. There was considerable clinical cardiomegaly, right ventricular in type. A grade 3/6 pansystolic mur-

FIG. 3. Case 1. The heart has been opened to show the pulmonary artery (left) and aorta (right) lying side by side. The aortic valves are normal and there are no pulmonary valves. The channel between right ventricle and pulmonary artery is completely obstructed (arrow). The small main pulmonary artery with the pulmonary sinuses ends blindly.

mur could be heard over the whole of the front of the chest, maximal in the fourth left and right parasternal spaces and radiating to the right lower chest. A loud triple rhythm was audible and the second sound appeared single. The hemoglobin was 19 gm. per cent.

The electrocardiogram (Fig. 1B) showed right axis deviation (+160°) with a clockwise loop in the frontal plane. Right atrial enlargement was best shown in V_1 where the P wave was 6 mm. in height. A qR complex was present in V_1 with a Q wave of 4.5 mm. and an R wave of 8.5 mm. The T wave was inverted. The intrinsicoid deflection was 0.05 second. An RS complex was present in V_6 and V_7.

X-ray examination showed striking cardiomegaly (Fig. 2B) consisting mainly of an aneurysmal right atrium. The visible lung fields were extremely oligemic.

The course was rapidly downhill with death in forty-eight hours.

At necropsy, the abnormal findings were confined to the heart which was extremely large, weighed 44 gm. and almost filled the entire chest cavity. The right atrium was aneurysmal and the right ventricle was considerably enlarged. The pulmonary arteries were small and narrow and there was no communication between the main pulmonary artery and the right ventricular cavity. The pulmonary valves were formed but were completely stenosed. A narrow patent ductus was present and there was an ostium secundum defect between the atria. The semilunar valves appeared to be within normal limits but incompetence of the tricuspid valve due to extreme dilatation of the right-sided heart chambers appeared to be present. Compression of both lungs by the greatly enlarged heart was noted.

CASE 3. B. N., a male Bantu infant one day old, was admitted extremely dyspneic, distressed and severely cyanosed. Edema of the eyes and feet was present and the liver was palpable below the costal margin. The pulse rate was 150 per minute; the extremities were warm, and the respirations were rapid. The heart on palpation occupied most of the chest and a pansystolic murmur was audible centrally, although best heard in the fourth left and right parasternal spaces. The hemoglobin was 18.5 gm. per cent.

The electrocardiogram (Fig. 1C) showed right axis deviation (+100°) with clockwise rotation in the frontal plane. Right atrial enlargement was present, with a P wave of 4 mm. in lead II. There was a Q wave of 4 mm. and an R of 6 mm. in V_1 with an intrinsicoid deflection of 0.04 and slight T wave inversion. The R and S waves were equiphasic in V_6 and there was no Q wave.

Chest x-ray examination (Fig. 2C) showed gross cardiac enlargement with the heart occupying most of the chest. Aneurysmal dilatation of the right atrium was responsible for most of the cardiomegaly. The lung fields which were not obscured by the cardiac shadow appeared to be oligemic.

The child died within a few hours of admission.

At necropsy, an enormous heart was found occupying the whole of the anterior portion of the chest cavity with compression of both lungs. Aneurysmal dilatation of the right atrium was present with tricuspid incompetence and a furled, thickened, posterior valve cusp. The pulmonary artery was completely stenosed at the valve cusps and there was no communication between the pulmonary artery and the right ventricular cavity. The right ventricle was hypertrophied, the ductus arteriosus was patent and an atrial septal defect was present.

CASE 4. L. K., a colored female infant of eight days, was admitted with a history of cyanosis and dyspnea since birth.

On examination, the child was centrally cyanosed (grade 3) but normally formed. The pulses appeared normal and the liver was not enlarged. The heart was markedly increased in size, the apex was right ventricular in type. A striking triple rhythm was audible at all areas with a grade 3 pansystolic murmur maximal at the fourth space to the right and left of the sternum and radiating well to the lower right side of the chest. The second sound appeared to be single.

The electrocardiogram (Fig. 1D) showed right axis deviation (+100°) with clockwise rotation in the frontal plane and "incomplete right bundle branch block." Marked right atrial enlargement was present, with a P wave of 3.5 mm. in lead II and 4 mm. in V_1. In V_1 there was a Q wave of 3.5 mm., an

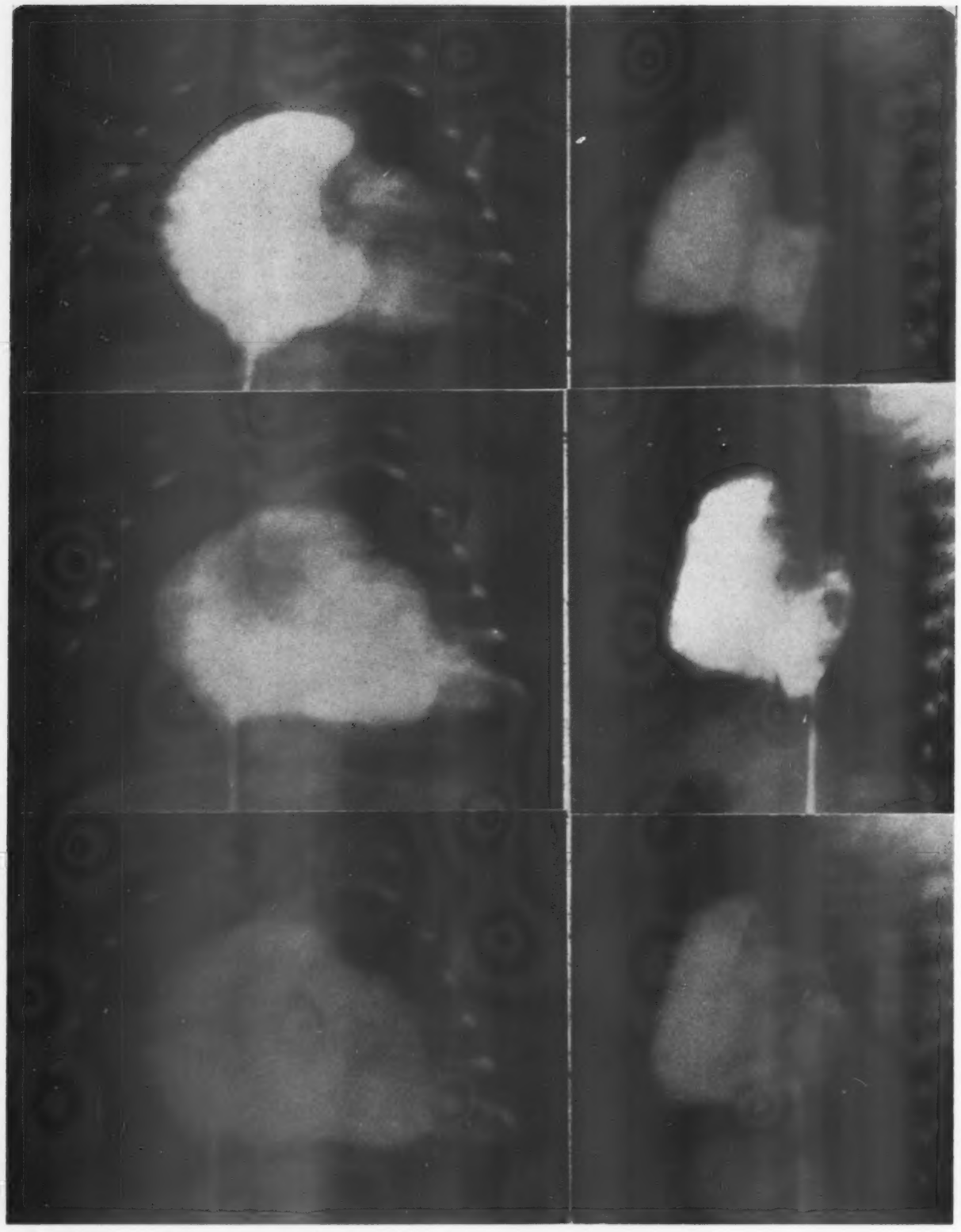

FIG. 4. Case 4. Simultaneous A–P and left lateral angiograms from the right atrium. In the top panel dye has entered the aneurysmal right atrium, the left atrium and the right ventricle. There is no dye in the pulmonary artery. The middle panel shows dye filling the right atrium, left atrium, right and left ventricles. The bottom panel now shows filling of the aorta and the pulmonary artery. Subsequent films showed good opacification of the aorta with late filling of the small pulmonary arteries.

R wave of 7 mm. and an S wave of 5 mm., and the T wave was inverted. The S wave in V_6 was broad, but the amplitude of the R and S waves was equal.

X-ray examination (Fig. 2D) showed considerable cardiomegaly with the heart occupying most of the chest cavity. The enlargement consisted largely of right atrium and the superior vena cava was prominent. The lung fields were oligemic.

Angiocardiogram: A simultaneous A-P and lateral angiocardiogram was performed after catheterization of the right atrium via the femoral vein (Fig. 4). The early films showed dye entering an enormous right atrium with slight filling of the right ventricle. Opacification of the left atrium and left ventricle through an atrial septal defect then appeared with filling of the aorta and pulmonary arteries. The aorta was well filled but the pulmonary arteries were small. Filling of the pulmonary arteries from the right ventricle was not shown.

Surgical Findings: A diagnosis of pulmonary atresia was made and surgical treatment was advised. At surgery, a very large patent ductus was found entering the pulmonary artery from the aorta in the usual situation. The pulmonary valves were normal and the pressure in the pulmonary arteries appeared to be elevated. An enormous right atrium was present with tricuspid incompetence. The ductus was ligated and the atrial septal defect repaired but the patient did not survive long after surgery. An Ebstein's anomaly was suspected.

At necropsy, aneurysmal dilatation of the right atrium was found with tricuspid incompetence and anomalous insertion of the tricuspid valve (Ebstein's anomaly) (Fig. 5). The tricuspid valve was inserted low down in the right ventricle, practically occluding the ventricular system. The pulmonary valves were normally formed; the pulmonary arteries were small. The ductus arteriosus had been ligated and the atrial septal defect repaired. Some collapse of the lungs was present.

FIG. 5. Case 4. The abnormal displaced tricuspid valve with its chordae (arrow) can be seen inserted into the right ventricle. Part of the right ventricle is incorporated into the right atrium and the true right ventricular chamber is small.

COMMENTS

Pulmonary atresia with intact ventricular septum is a rare condition. Life expectancy is very poor unless surgical correction can be achieved. The majority of infants with this condition die at a very early stage. In our series, two patients were dead within a week, the oldest surviving to two months. In rare cases the presence of a large patent ductus arteriosus can maintain life, in one patient[16] to fifteen years, and in another to twenty. There is no particular sex incidence, although two of our three patients were female.

Complete obstruction to blood flow from right ventricle to pulmonary artery is the fundamental disturbance in this condition. Life is maintained by flow of blood from right atrium to left atrium and left ventricle. The entire volume of circulating blood is discharged by the left ventricle into the aorta, and survival depends upon the presence of a patent ductus arteriosus.[14,15]

Anatomic Findings: In the first three cases the obstruction to pulmonary blood flow was due to organic occlusion at the orifice of the main pulmonary artery. Two of these (Case 2 and 3) showed the characteristic anatomic finding of an imperforate diaphragm across the pulmonary valve ring consisting of the fused pulmonary valves. The third (Case 1) was unusual in that the pulmonary valves were absent. All three cases showed marked hypertrophy and dilatation of the right ventricle, suggesting the presence of incompetent tricuspid valves. In Case 3, there was actual anatomic deformity of the septal leaflet of the tricuspid valve, preventing adequate valve function. Confirmation

of the presence of tricuspid incompetence was found in the presence of gross right atrial enlargement; in fact, the right atrium in each case was aneurysmal, dwarfing all the other cardiac chambers. An atrial septal defect of the secundum type was present in all three cases and a narrow patent ductus communicated with the normally formed but diminutive pulmonary arteries.

In the fourth case obstruction to blood flow from right ventricle to pulmonary artery was entirely functional. The pulmonary valves were normally formed and competent with a normal valve ring and orifice. Two factors were thought to be responsible. First, Ebstein's anomaly of the tricuspid valve was present, leading to gross tricuspid incompetence and aneurysmal dilatation of the right atrium. Also, by the very nature of the Ebstein's anomaly, right ventricular muscular function is impaired. The presence of a considerably enlarged patent ductus arteriosus was the second important contributory factor. The ductus was of such size that aortic pressure was directly transmitted to the pulmonary arteries, keeping the pulmonary valves closed during right ventricular systole as well as diastole and thus preventing blood flow from right ventricle to pulmonary artery. The fetal circulation was presumably very little different, with blood from the right atrium deviated across the atrial septum to the left ventricle and thence to the aortic and pulmonary arteries. An atrial septal defect and a foramen ovale were, in fact, present, allowing easy access to the left atrium.

Clinical Features: Physical development and nutrition during fetal life is normal; at birth all our patients appeared to be healthy. Cyanosis was observed in the first case only after two months but in the others it was noted soon after birth. Respiratory distress was a constant feature. On examination, central cyanosis was present in all cases. It was moderate and equal in the upper and lower extremities. Clubbing of the fingers and toes was not noted.

Jugular venous distension and pulsation is always difficult to assess in infants and these patients were no exception. Mild hepatomegaly and edema were noted in only one case. The peripheral pulses were all within normal limits. Palpation of the chest revealed considerable cardiomegaly, in all cases right ventricular in type. Unlike Keith et al.,[7] we found a loud systolic murmur in all cases, the nature and radiation of which was helpful in diagnosis. The murmur was pansystolic, blowing in character and maximal to the right and left of the lower sternum, radiating well to the right side of the chest. The murmur in character and position was quite compatible with incompetence of the tricuspid valve, confirmed at necropsy in every case. A widely-heard triple rhythm with accentuation of the third sound completed the auscultatory findings. Neither splitting of the second sound nor a continuous murmur[7,14] was audible in any case.

Electrocardiographic Features: The electrocardiogram in all cases showed evidence of right atrial and right ventricular hypertrophy. Tall, peaked P waves were particularly prominent either in the limb leads or the precordial leads. Right axis deviation was present in every case, varying from $+100°$ to $160°$ with a clockwise loop in the frontal plane. There was no evidence of left ventricular enlargement, S waves persisting up to V_7, and there were no voltage changes. The electrocardiogram, however, was the only way in which the cases with organic pulmonary atresia differed from the case with functional pulmonary atresia. The three patients with organic pulmonary atresia all showed electrocardiographic evidence of right ventricular enlargement with a qR complex in V_3R and V_1, whereas a QRS complex with the pattern of "incomplete right bundle branch block" was present in the case with functional pulmonary atresia. The presence of qR complexes in the right precordial leads, especially in Case 4, supports the view of Sodi-Pallares et al.[16] that this pattern provides a good indication of right atrial dilatation.

Radiographic Features: The radiologic appearances were fairly characteristic in all four cases. Gross cardiomegaly was the rule with cardiothoracic ratios of from 82 to 85. Aneurysmal dilatation of the right atrium was chiefly responsible for the increase in the cardiac shadow, enlargement of the right ventricle being less easily determined in the presence of such giant right atria. However, the outflow tract of the right ventricle was prominent in the A-P view, producing a convex left border. In the lateral views the enlargement of the right-sided chambers was equally striking so that the retrosternal space was occupied by the right atrial shadow. Because of the cardiomegaly very little lung field could be seen but what was visible was clearly oligemic.

Angiocardiography was performed in one case

(Case 4) with functional pulmonary atresia, but the same changes would be expected in the others. Injection of contrast medium into the right atrium showed immediate filling of the aneurysmal right atrium in the biplane A-P and lateral pictures. The right ventricle was less well outlined but ended bluntly, with no dye entering the main pulmonary artery. Passage of the radiopaque material from right atrium to left atrium and left ventricle then occurred and the aorta was well outlined. The pulmonary arteries were diminutive and filled in the later pictures, presumably from the aorta. The films were not technically good enough to outline the ductus. A cineangiocardiographic study[10] has shown similar findings.

Differential Diagnosis: The diagnosis of pulmonary atresia with tricuspid incompetence must be differentiated from severe pulmonary stenosis with intact ventricular septum and tricuspid atresia. The electrocardiographic and radiologic findings excluded the latter. The site of maximal intensity of the systolic murmur and the radiation to the right side of the chest favors tricuspid incompetence and pulmonary atresia. However, in pulmonary valve stenosis and infundibular stenosis the murmur may have similar characteristics, duration, intensity and position.[16] The behavior after amyl nitrite inhalation is the same. Moreover, in some cases of severe pulmonary stenosis with intact ventricular septum, especially in infancy, signs suggestive of tricuspid incompetence occur making accurate differentiation impossible. The diagnosis can thus be made with certainty only by angiocardiography. Surgery should be advised in either instance.

The occurrence of functional pulmonary atresia must be extremely rare and to our knowledge this is the first case recorded. Only the combination of a large ductus with severe Ebstein's anomaly makes this condition possible. The clinical and hemodynamic findings are identical. The only point of departure was the electrocardiogram which showed a QRS pattern in V_1 and slurring of the terminal S waves in the left precordial leads.

Summary

1. Pulmonary atresia with intact ventricular septum is a rare anomaly and is usually fatal within the first few weeks of life.

2. The fundamental defect is complete obstruction of the pulmonary valve, the circulation being maintained by blood flow from right atrium to left atrium. The left ventricle functions as a single ventricle; a mixed venous and arterial blood is ejected from the ventricle into the aorta. Life depends on the size of the patent ductus from which the total pulmonary circulation is derived.

3. The competence of the tricuspid valve determines the size of the right ventricle. When the valves are competent the right ventricular chamber is small and the walls hypertrophied. When the valves are incompetent the right ventricle is dilated and hypertrophied.

4. Three cases of pulmonary atresia with intact ventricular septum and tricuspid incompetence are described. Cyanosis and dyspnea were associated with considerable cardiomegaly, a triple rhythm and a loud pansystolic murmur maximal at the lower sternal edge radiating to the lower right side of the chest. The electrocardiogram showed severe right atrial hypertrophy and right ventricular hypertrophy with a qR complex in V_1. Radiologically, the heart was grossly enlarged with aneurysmal dilatation of the right atrium, right ventricular enlargement and marked pulmonary oligemia.

5. One case of functional pulmonary atresia with intact ventricular septum is described, due to a combination of Ebstein's anomaly of the tricuspid valve and a very large patent ductus arteriosus. The clinical picture was identical with organic pulmonary atresia except for the electrocardiogram, which showed a QRS pattern in V_1 with slurring of the terminal S in the left precordial leads. An angiocardiographic study from the right atrium showed late filling of the pulmonary arteries from the aorta after passage of opaque medium from the aneurysmal right atrium to the left atrium and left ventricle.

Acknowledgment

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References

1. Hunter, J. M. Cited in reference 5.
2. Lordat (1882). Cited in reference 5.
3. Hare, C. J. Cited in reference 7.
4. Rokitansky, C. F. Cited in reference 5.
5. Peacock, T. B. Cited in reference 7.
6. Abbott, M. E., Lewis, D. S. and Beattie, W. W.

Differential study of a case of pulmonary stenosis of inflammatory origin (ventricular septum closed) and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated ventricular septal defect and death from paradoxical cerebral embolism. *Am. J. M. Sci.*, 165: 636, 1923.

7. KEITH, J. O., ROWE, R. D. and VLAD, P. Heart Disease in Infancy and Childhood, p. 569. New York, 1958. The MacMillan Co.
8. NOVELO, S., CHAIT, L. O., ZAPATA DIAZ, J. and VELAZQUEZ, T. Atresia pulmonary estenosis tricuspidea sin communicacion interventricular. *Arch inst. cardiol. Mexico*, 21: 325, 1951.
9. GREENWOLD, E. W., DUSHANE, J. W., BURCHELL, H. B., BRUWER, A. and EDWARDS, J. E. Congenital pulmonary atresia with intact ventricular septa. Two anatomic types. Proceedings of the 29th Scientific Sessions of the American Heart Association, (Oct.) 1956, p. 51.
10. PAUL, M. H. and LEV, M. Tricuspid stenosis with pulmonary atresia. A cineangiographic-pathologic correlation. *Circulation*, 22: 198, 1960.
11. EDWARDS, J. E. Pulmonary atresia with intact ventricular septum. In: Pathology of the Heart, p. 397. Edited by Gould, S. E. Springfield, Illinois, 1959. Charles C Thomas.
12. BROWN, J. W. Congenital Heart Disease, 2nd edition, p. 138. London, 1950. John Bale, Ltd.
13. GLABOFF, J. J., GOHMANN, J. T. and LITTLE, J. A. Atresia of the pulmonary artery with intact ventricular septum. *J. Paediat.*, 37: 390, 1950.
14. ALLANBY, K. D., BRINTON, W. D., CAMPBELL, M. and GARDNER, F. Pulmonary atresia and the collateral circulation to the lungs. *Guy's Hosp. Rep.*, 99: 110, 1950.
15. COSTA, A. Cited in reference 7.
16. SODI-PALLARES, D., BISTENI, A. and HERRMANN, G. R. Some views on the significance of qR and QR type complexes in right precordial leads in the absence of myocardial infarction. *Am. Heart J.*, 43: 716, 1957.
17. SCHRIRE, V. and SUTIN, G. J. Personal observations, 1960.

Coarctation of the Pulmonary Artery and Pulmonary Valvular Stenosis*

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THE SKODAIC THEORY of the etiology of coarctation of the aorta postulates that coarctation is produced by an extension of the obliterating tissue from the ductus arteriosus into the aortic wall. Since a coarctation of the pulmonary artery has never been observed at the pulmonary end of the ligament of the ductus arteriosus, it has been argued that the hypothesis is not tenable.[1]

Since 1953, several cases have been described with a narrowing not only in the pulmonary artery at the origin of the ductus arteriosus but also peripherally in the branches of the pulmonary artery. Söndergaard[2] reported three cases, all of which had a pulmonary valvular or infundibular stenosis and a narrowing of the pulmonary artery at the bifurcation. The author called the last-mentioned anomaly "coarctation of the pulmonary artery." Schumacher and Lurie[3] and Coles et al.[4] have each described one case of pulmonary valvular stenosis in combination with a coarctation of the pulmonary artery. Powell[5] described a similar case in which there was no evidence of a pulmonary valvular stenosis but this lesion could not be excluded with certainty.

Vermillion[6] described two cases, one with a ventricular septal defect and the other with a pulmonary valvular stenosis, both having a narrowing of the right pulmonary artery. Similar peripheral narrowings have been described in ever increasing number since Oppenheimer[7] reported the first case of multiple narrowings of the pulmonary artery. Thus, Arvidsson et al.[8] contributed two cases; Gyllensvärd et al.[9] described eight cases including one or two with a narrowing at the bifurcation; and D'Silva et al.,[10] ten cases.

In 1959 Shafter and Bliss[11] made a survey of all published reports of cases of narrowing or stenosis of the pulmonary artery and found thirty-three such cases. They described an additional five cases. In four of these the diagnosis was made by catheterization of the heart without angiocardiography; because of this it is difficult to define the exact anatomic position of the stenosis. Trower et al.[12] have recently published two cases, one of which was successfully corrected under hypothermia.

Thus, a review of the literature has shown that several cases have been diagnosed by catheterization alone without angiocardiography. We have observed one case in which catheterization did not give the diagnosis but angiocardiography did.

CASE REPORT

The patient was a twenty-one year old carpenter with heart disease diagnosed at school. He had never been cyanotic but had always complained of breathlessness on exertion, but not during routine work.

Examination in 1957 showed a patient of normal body build (and normal strength) without cyanosis or dyspnea at rest. A slight precordial bulging was found and a systolic murmur (grade 4) over the pulmonary area as well as a thrill and an accentuated pulmonary second sound. The electrocardiogram (Fig. 1) showed normal axis deviation with a QRS duration of 0.11 second. P waves were prominent but not definitely increased above normal values. In the precordial leads marked signs of right ventricular preponderance were found. The roentgenologic examination (Fig. 2) showed slight enlargement of the heart, especially of the right ventricle, with a relative volume of 690 cc. per square M. of body surface (Liljestrand[13]) and dilatation of the pulmonary artery. The pulmonary vasculature was sparse.

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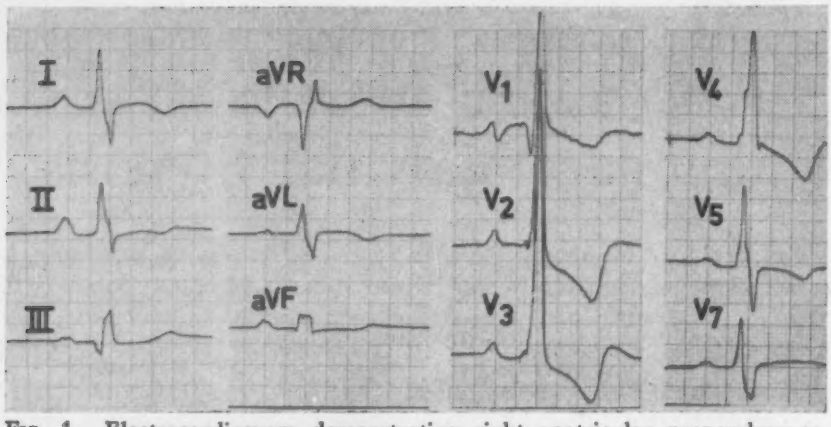

FIG. 1. Electrocardiogram demonstrating right ventricular preponderance.

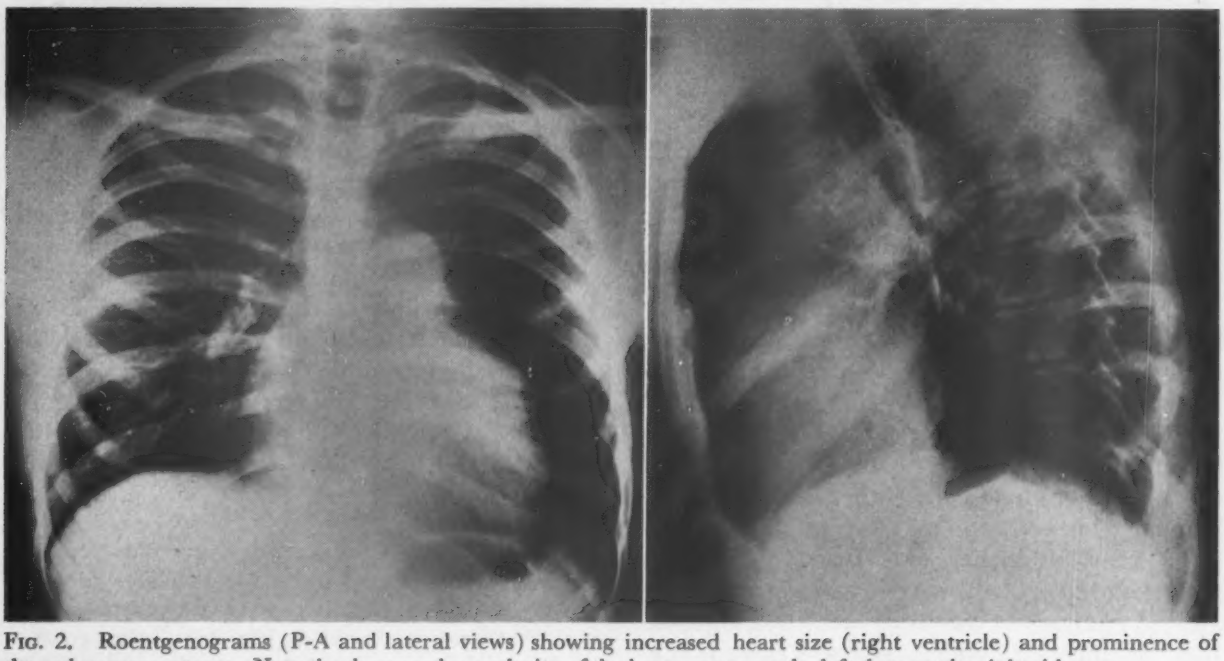

FIG. 2. Roentgenograms (P-A and lateral views) showing increased heart size (right ventricle) and prominence of the pulmonary artery. Note the decreased vascularity of the lungs, more on the left than on the right side.

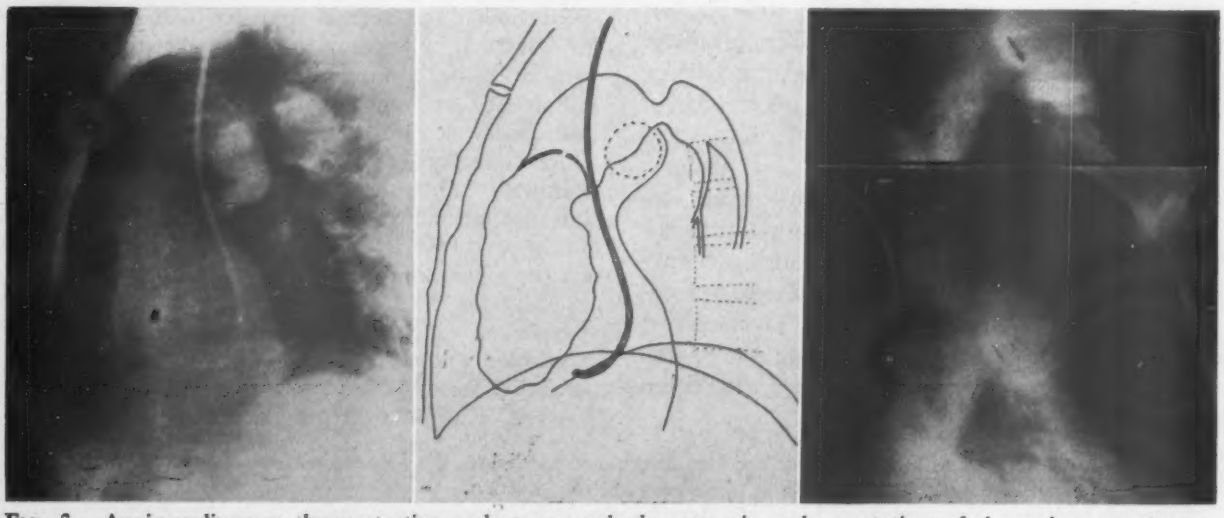

FIG. 3. Angiocardiogram demonstrating pulmonary valvular stenosis and coarctation of the pulmonary artery.

Right heart catheterization showed a mean pressure of 7 mm. Hg in the right atrium, 181/0 in the right ventricle and 26/8 in the pulmonary artery with a mean pressure of 11 mm. Hg. Pressure was measured in the right pulmonary artery (8–11 mm. Hg) but not in the left branch. Pulmonary capillary venous pressure was 6 mm. Hg. There were no signs of left to right shunt and there was normal oxygen saturation in the brachial artery.

Angiocardiography showed a narrowing of the left pulmonary artery at the pulmonary end of the ductus arteriosus and also a pulmonary valvular stenosis (Fig. 3).

Operative Findings: The patient was operated upon with a left-sided posterolateral incision and resection of the fourth rib. The right ventricle was extremely enlarged and the pulmonary artery dilated. The coarctation of the left pulmonary artery was marked and there was no patent ductus. Surgical relief of the coarctation was not considered necessary. A transventricular dilatation of the pulmonary valve was made with Brock's dilator, and the systolic pressure in the right ventricle fell promptly from 130 to 75 mm. Hg; the mean pressure in the pulmonary artery rose from 7 to 27 mm. Hg. The postoperative period was uncomplicated.

Re-examination one year later revealed that the heart volume had diminished. The electrocardiogram showed no further changes and the patient was in good health.

Comments

In the literature there are to be found at least five cases with a proved narrowing of the pulmonary artery at the pulmonary end of the ligament of the ductus arteriosus in combination with a pulmonary infundibular or valvular stenosis. The pressure gradient between the right ventricle and the pulmonary artery in some of these cases was extremely high. For the diagnosis it is important to make pressure recordings from both the right and left pulmonary artery and to perform angiocardiography.

The combination of these two anomalies is remarkable.[4] Can the pulmonary valvular stenosis have any connection with the development of the coarctation of the pulmonary artery? If the pulmonary blood flow is low, can it result in premature closure of the ductus arteriosus with consequent overcontraction at the origin of the ductus and subsequent stricture of the pulmonary artery at that level? There is no adequate answer, as we do not know the mechanism underlying the closing procedure,[14] but if there is such a connection the combination of a pulmonary valvular stenosis and a patent ductus ought to be rare. Ekström found three patients with pulmonary valvular stenosis and a pressure gradient of more than 30 mm. Hg out of 290 patients with patent ductus. Thus, the combination of a pulmonary valvular stenosis and a patent ductus with a high pressure difference across the pulmonary valve is rare.[14] On the other hand, if a high pulmonary resistance may be established at birth, the frequency of patent ductus ought to be high according to this theory. In 115 cases of patent ductus, Wood[14] found an Eisenmenger reaction (bidirectional or reversed shunt) in 13.3 per cent. Thus, the combination of a high pulmonary resistance and a patent ductus seems to be fairly common.

We believe that we can neither exclude the possibility of a connection between valvular pulmonary stenosis and coarctation of the pulmonary artery nor exclude the skodaic theory on the basis of the fact that we have not observed any coarctation at the pulmonary end of the ligament of ductus arteriosus, as such cases are observed.

Summary

A case is reported of coarctation of the pulmonary artery at the pulmonary end of the ligament of the ductus arteriosus in combination with a pulmonary valvular stenosis. The valvular stenosis was operated on with Brock's dilator with good result.

The combination of these two malformations and the possibility of a high pressure difference between the right ventricle and the pulmonary artery as a possible cause of coarctation are briefly discussed.

References

1. Edwards, J. E. Congenital malformations of the heart and great vessels. In: Gould, S. E.: Pathology of the Heart, p. 453. Springfield, Illinois, 1959. Charles C Thomas.
2. Söndergaard, T. Coarctation of the pulmonary artery. *Danish M. Bull.*, 1: 46, 1954.
3. Schumacher, H. B. J. and Lurie, P. R. Pulmonary valvulotomy: description of a new operative approach with comments about the diagnostic characteristics of pulmonic valvular stenosis. *J. Thoracic Surg.*, 25: 173, 1953.
4. Coles, J. E. and Walker, J. W. Coarctation of the pulmonary artery. *Am. Heart J.*, 52: 469, 1956.
5. Powell, M. L. and Hiller, H. G. Pulmonary coarctation. *M. J. Australia*, 1: 272, 1955.
6. Vermillion, M. B., Leight, L. and Davis, L. A. Pulmonary artery stenosis. *Circulation*, 17: 55, 1958.
7. Oppenheimer, E. Partial atresia of the main

branches of the pulmonary artery occurring in infancy and accompanied by calcification of the pulmonary artery and aorta. *Bull. Johns Hopkins Hosp.*, 63: 261, 1938.

8. Arvidsson, H., Karnell, J. and Möller, T. Multiple stenosis of the pulmonary arteries associated with pulmonary hypertension, diagnosed by selective angiocardiography. *Acta radiol.*, 44: 209, 1955.
9. Gyllensvärd, A., Lodin, H., Lundberg, Å. and Möller, T. Congenital multiple peripheral stenosis of the pulmonary artery. *Pediatrics*, 19: 399, 1957.
10. D'Silva, J. L., Gasul, B. M. and Dillon, R. F. Stenosis of the right main pulmonary artery. *Circulation*, 21: 1116, 1960.
11. Shafter, H. A. and Bliss, H. A. Pulmonary artery stenosis. *Am. J. Med.*, 26: 517, 1959.
12. Trower, W. B., Abelman, W. H. and Harken, D. E. Surgical correction of coarctation of the main pulmonary artery. *Circulation*, 21: 672, 1960.
13. Liljestrand, G., Lysholm, E., Nylin, G. and Zachrisson, C. G. The normal heart volume in man. *Am. Heart J.*, 17: 406, 1939.
14. Wood, P. Diseases of the Heart and Circulation, 2nd edition, pp. 380, 394 and 408. Philadelphia. J. B. Lippincott Co.

Absence of the Pulmonary Valve

Report of Two Cases Associated with Other Congenital Lesions*

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THE COMPLETE, CONGENITAL absence of the pulmonary valve is rare. Only ten cases proved at autopsy have been thus far reported, and most were associated with other congenital malformations. The following is a description of two other instances of absence of the pulmonary valve, of which one was associated with an infundibular pulmonic stenosis and a ventricular septal defect and the other with an aneurysm of an aortic sinus of Valsalva.

CASE REPORTS

CASE I. G. F., a sixteen month old boy, was admitted to Maisonneuve Hospital on November 14, 1959, for treatment of furunculosis. It was reported that cyanosis had been present during the first week of life but had subsequently disappeared. He had been treated numerous times at another hospital for infections of the upper respiratory tract, and attacks of dyspnea and cyanosis. In October 1958, a left superior lobectomy had been performed at another hospital.

Physical Examination: His weight was 15 pounds, 6 ounces. He appeared chronically ill and underdeveloped. There was slight cyanosis but no clubbing. He had a pectus carinatum. Overlying a left-sided thoracotomy scar were five small furuncles and a small subcutaneous abscess. Bronchial rales were disseminated over both lung fields. The heart rhythm was regular at 110 per minute and the blood pressure was 100/64 mm. Hg. A to and fro murmur, grade 3–4, was heard maximally at the left second and third intercostal spaces near the sternum. A single second heart sound was audible at the base, loudest over the second right intercostal space. The liver extended over 1 fingerbreadth below the right costal margin. No edema was present.

The roentgenogram of the thorax (Fig. 1) revealed osteolytic lesions of the left fifth rib compatible with osteomyelitis. The left upper lung field showed emphysematous changes. Lesions localized in the right upper lobe compatible with bronchopneumonia were also described. The heart was enlarged and the cardiothoracic ratio measured 9.7 by 14.7 cm. The pulmonary artery appeared greatly dilated and was described as pulsatile at fluoroscopy. The pulmonary vasculature was otherwise normal. The *electrocardiogram* (Fig. 2) showed right axis deviation, right ventricular hypertrophy and an rsR′ configuration in V_1-V_2. Routine laboratory tests were normal except for a red blood cell count of 3,920,000 and a white blood cell count of 16,300.

Cardiac Catheterization and Angiocardiography: On January 5, 1960, cardiac catheterization and angiocardiography were performed under anesthesia by rectal Pentothal. The cardiac catheterization data shown in Table I suggested pulmonary stenosis and a ventricular septal defect with a bidirectional shunt. The catheter was introduced from the right ventricle into the aorta. The withdrawal pressure recording from the pulmonary artery to the right ventricle (Fig. 3) showed a single gradient at the usual level of the pulmonary valve, compatible with pulmonary valvular stenosis. A selective angiocardiogram (Fig. 4) showed early visualization of the aorta, a ventricular septal defect and a localized area of constriction of the distal outflow tract suggesting pulmonary valvular stenosis.

After the procedures, which seemed to have been well tolerated, the infant remained unconscious and rapid breathing developed. Right-sided convulsions appeared and he died twenty-four hours later without having recovered consciousness.

Autopsy Findings: The heart was moderately enlarged; the weight was not obtained because the lungs were not removed. Measurements of the pertinent structures are listed in Table II. The interatrial septum was intact. An infundibular stenosis was located at 8 mm. below the pulmonic ring. This consisted of a muscular band measuring 6 mm. in width and 1 cm. in thickness, covering two-thirds of the circumference over the posterior and lateral walls. No semilunar valve was identified

* From the Institute of Cardiology of Montreal.

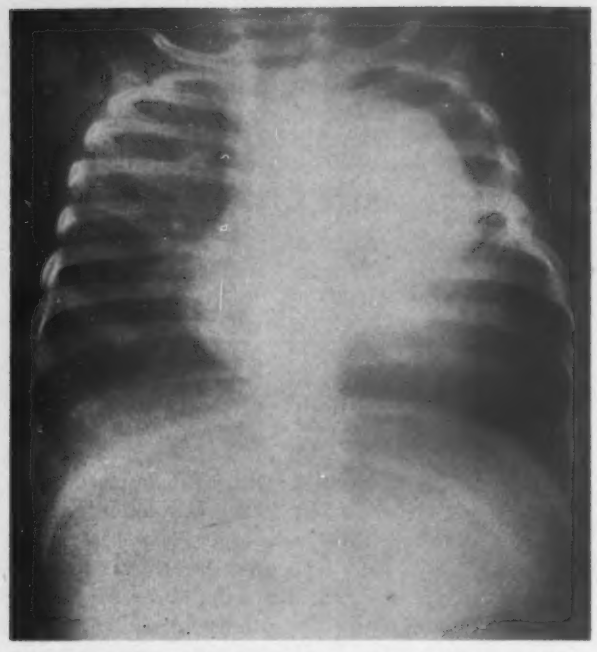

FIG. 1. Case 1. Posteroanterior roentgenogram of the thorax. Note the greatly dilated pulmonary artery.

(Fig. 5). A thin, irregular rim of tissue extended over the posterior wall and two excrescences of a few millimeters in diameter were found on the anterolateral walls at the level of the pulmonic ring. Smooth thickenings of several millimeters were observed below the pulmonic ring. A high ventricular septal defect and an overriding aorta were noted. The main and left pulmonary arteries were grossly dilated. The venae cavae and pulmonary veins were normally connected. The tricuspid, mitral and aortic valves were normal. The aortic arch was in a normal position and the ductus arteriosus was

TABLE I

Case 1. Cardiac Catheterization Data

Site of Catheter	Pressure (mm. Hg)	Oxygen Saturation (per cent)
Superior vena cava	...	60
Inferior vena cava	...	60
Right atrium	3/0	54
Right ventricle, low	76/2	68
Right ventricle, high	74/3	78
Main pulmonary artery	28/10	67
Right pulmonary artery	23/7	66
Left pulmonary artery	20/8	66
Right pulmonary artery (wedge)	5/0	...
Aorta (through ventricular septal defect)	81/43	82.5

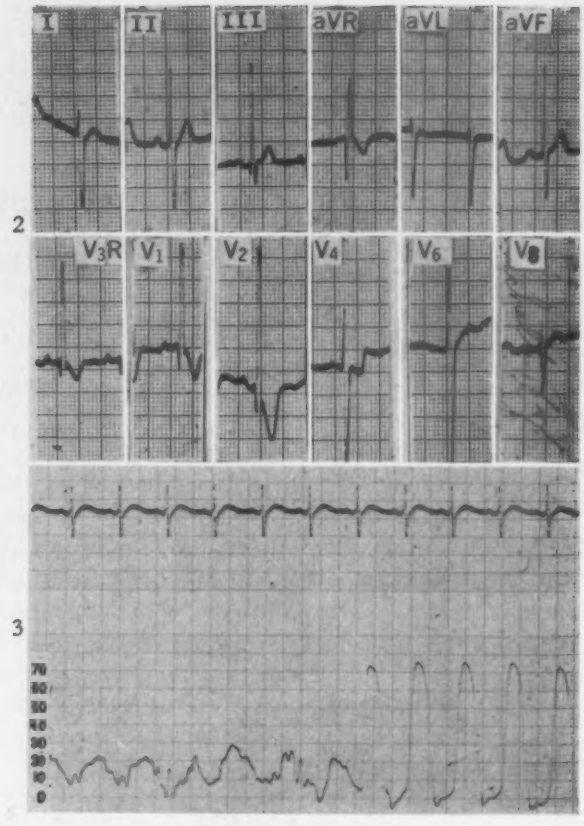

FIG. 2. Case 1. Electrocardiogram showing right ventricular hypertrophy and an rsR′ configuration in lead V_1-V_2.

FIG. 3. Case 1. Right heart catheterization. Withdrawal pressure recording from pulmonary artery to right ventricle, showing a single gradient at the usual level of the pulmonary valve.

TABLE II

Case 1. Measurement of Heart Structures at Autopsy

Structure	Measurement (cm.)
Pulmonic ring (diameter)	1.2 (1.12 ± 0.1)*
Aortic valve (diameter)	1.1
Right ventricular wall (thickness)	1
Left ventricular wall (thickness)	0.8
Interventricular septum (thickness)	1.2
Ventricular septal defect (diameter)	1
Main pulmonary artery (circumference)	8 (3.49 ± 0.4)*
Right pulmonary artery (circumference)	2.5
Left pulmonary artery (circumference)	10
Aorta (circumference)	4

* Normal measurement for a twelve to eighteen month old child. From: GOULD, G. E. Pathology of the Heart, p. 1064. Charles C Thomas.[9]

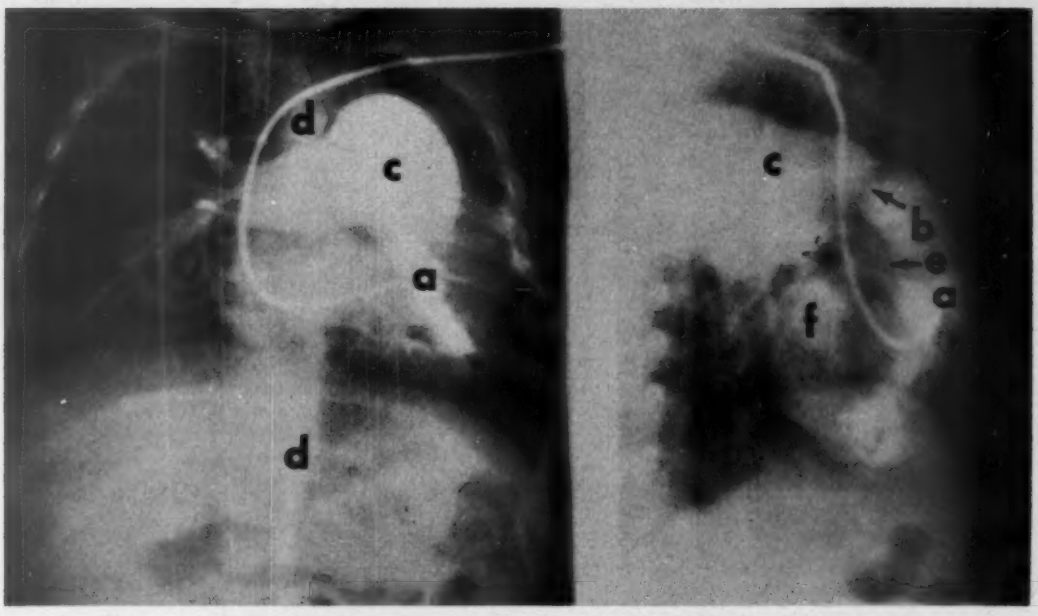

FIG. 4. Case 1. Angiocardiogram, two seconds after injection into the right ventricle. Anteroposterior (*left*) and lateral (*right*) views: a, right ventricle; b, localized constriction suggesting valvular stenosis; c, aneurysmal pulmonary artery; d, early filling of the aorta; e, ventricular septal defect; f, left ventricle.

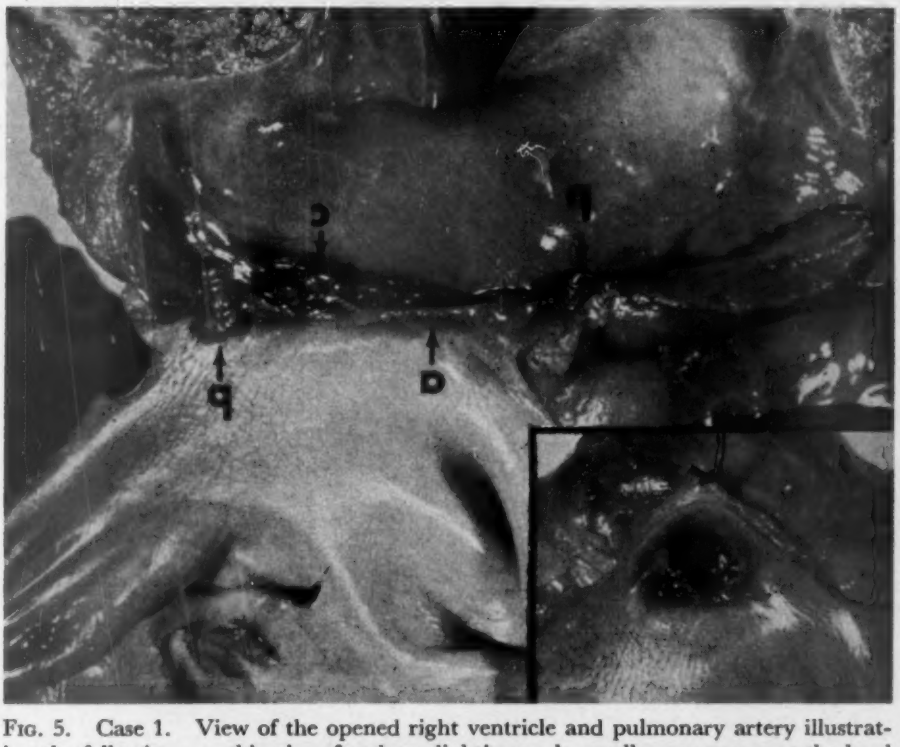

FIG. 5. Case 1. View of the opened right ventricle and pulmonary artery illustrating the following: a, thin rim of endocardial tissue; b, small excrescences at the level of the pulmonic ring; c, smooth thickenings below the pulmonic ring. *Insert* shows the view of the intact pulmonic orifice from above.

closed. The coronary arteries were normal. Other findings included an absent upper left lobe of the lung, passive congestion of the lungs and edema of the brain.

The histologic examination of the excrescences noted at the level of the pulmonic ring showed myxomatous connective tissue (Fig 6).

Comment: The antemortem diagnosis was valvular pulmonary stenosis and ventricular

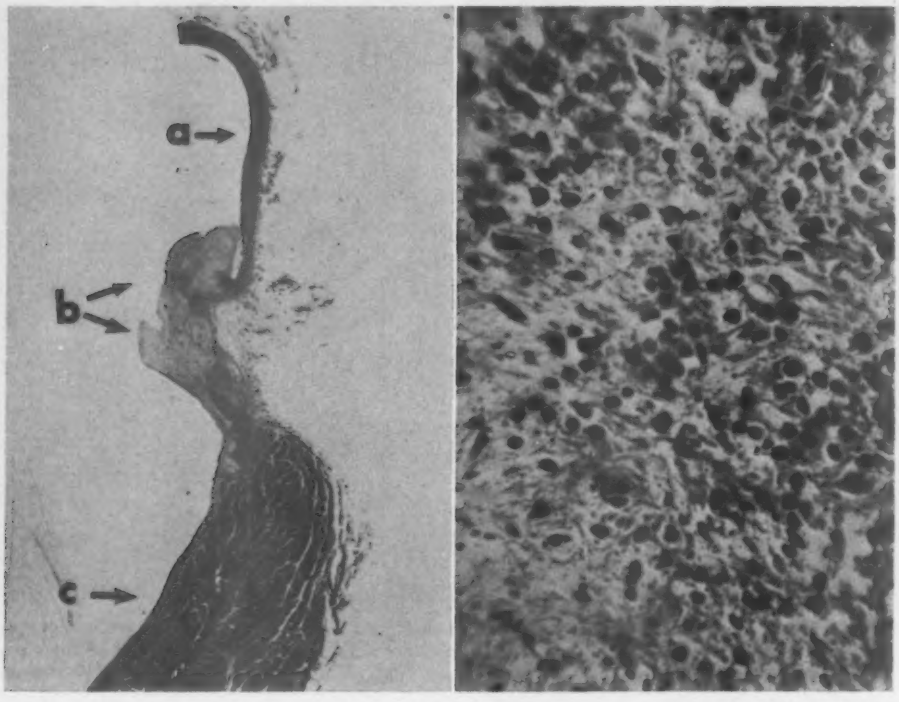

FIG. 6. Case 1. *Left:* Photomacrograph (×4) of the origin of the pulmonary artery and pulmonic ring section: a, pulmonary artery wall; b, excrescence and thickening at the level of the pulmonic ring; c, myocardium. *Right:* High power magnification (×200) of the excrescence showing the myxomatous connective tissue.

septal defect. The large pulsatile pulmonary artery was explained, although not satisfactorily, on the basis of a post-stenotic dilatation and a left to right shunt. The diastolic murmur, however, was puzzling. This patient was one of the five who died following cardiac catheterization, with or without selective angiocardiography, in a series of 1,218 examinations performed in this institution up to August 10, 1960.

CASE 2. M. T., a seven year old girl, was admitted on March 19, 1958. She seemed normal at birth and during early infancy. At four years of age she began to show exertional dyspnea which did not progress until six months before admission. She had an infection of the upper respiratory tract and subsequently complained of increasing orthopnea, dyspnea and edema. She became and remained bedridden. No cyanosis had been noticed.

Physical examination revealed an acutely ill girl weighing 39 pounds. The lips and finger nail beds were pink but the feet, including the toe nails, had a cyanotic hue. There was no clubbing. The jugular veins were distended and the carotid arteries were markedly pulsatile. The blood pressure at the arms was 180/60-0 mm. Hg and at the thighs, 200/80-40. The thorax had a normal appearance and the lungs were clear to percussion and auscultation. A systolic thrill was present over the second and third intercostal spaces near the sternum. A to and fro murmur was heard with a maximum intensity at the second and third intercostal spaces to the left of the sternum. The systolic component was widely transmitted to the anterior chest, neck and back. The diastolic murmur was shorter and variable in intensity. This to and fro murmur was described as continuous at times. The aortic second sound was of normal intensity but the pulmonic second sound was absent. The rhythm was regular and the heart rate was 120 per minute. The liver extended downward 4 fingerbreadths below the right costal margin. Ascites and edema of the legs were present.

The roentgenogram of the chest (Fig. 7) showed gross cardiomegaly with a cardiothoracic ratio of 16.5/19 cm. Both ventricles seemed enlarged. The lung vascularity was slightly increased. At fluoroscopy, the pulmonary artery segment was pulsatile. The *electrocardiogram* (Fig. 8) showed right axis deviation, marked right ventricular hypertropy and an rsR′ pattern in V_1-V_2. The routine laboratory tests were within normal limits except for albuminuria and a hemoglobin of 12.8 gm. per cent.

At right heart catheterization, a significant right ventricular-pulmonary artery pressure gradient was recorded but due to technical difficulties a pullback pressure tracing was not obtained and the type of pulmonary stenosis was not established (Fig. 9). The pressure in the pulmonary artery was 26/20 mm. Hg and the right ventricular pressure was

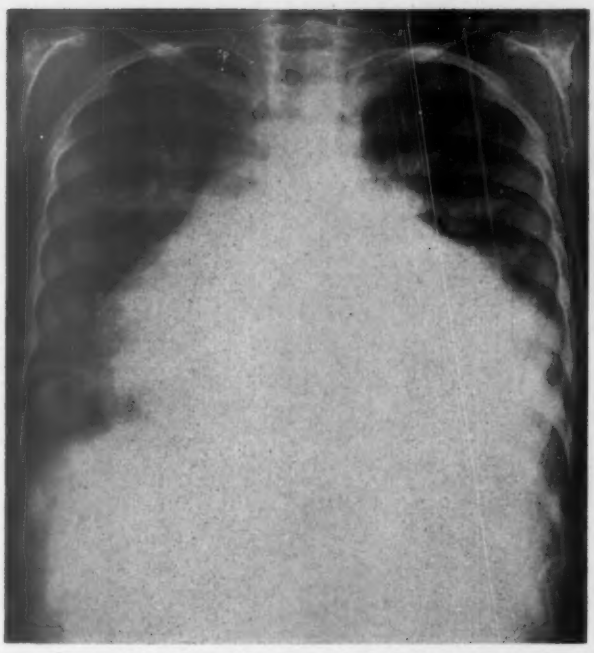

FIG. 7. Case 2. Posteroanterior roentgenogram of the chest showing generalized cardiac enlargement.

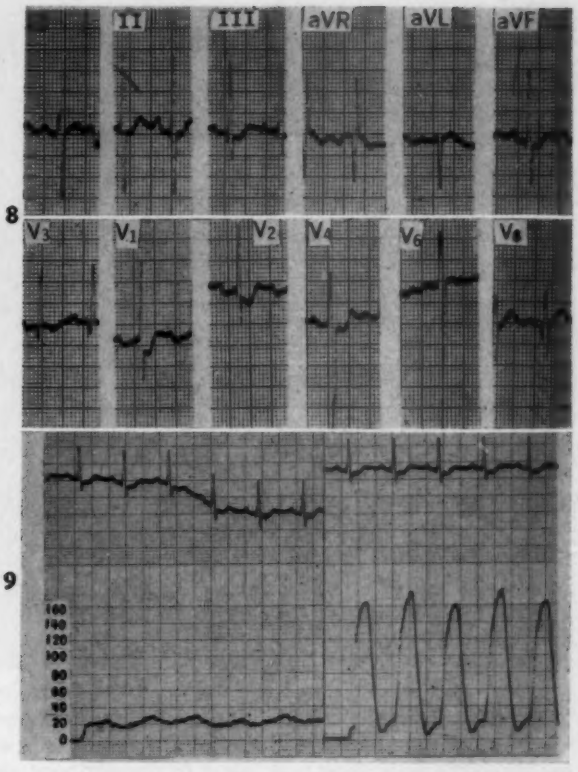

FIG. 8. Case 2. Electrocardiogram showing right ventricular hypertrophy and an rsR′ pattern in leads V_1-V_2.

FIG. 9. Case 2. Right heart catheterization. Discontinuous pressure record of the pulmonary artery (*left*) and right ventricule (*right*). The pulmonary artery diastolic pressure is equal to the right ventricular end diastolic pressure.

170/20 mm. Hg. The oxygen saturation values were ostensibly normal except for a difference of 0.4 vol. per cent (Van Slyke) or 3.5 per cent (cuvette oximetry) between the right ventricle and the pulmonary artery, a step-up of doubtful significance. Because of the precarious condition of the patient, the procedure had to be discontinued before an arterial oxygen saturation and pressure could be obtained. Angiocardiographic studies were not performed for the same reason.

The diagnosis considered was pulmonary stenosis with ventricular septal defect associated with aortic insufficiency. Because of a steadily downward course, a "salvage" operation was attempted but an unresponsive cardiac arrest occurred soon after the transventricular pulmonary valvotomy and dilatation of the infundibulum.

Postmortem Examination: The heart showed evidence of a right ventriculotomy. It was not weighed because the lungs were not removed from the specimen, but it was grossly enlarged. Both venae cavae drained normally. The foramen ovale was patent. The tricuspid valve appeared normal. The right ventricle was dilated and its walls measured 1 cm. at the greatest thickness. The infundibulum was not stenosed; at 1 cm. below the pulmonic ring it measured 1.5 cm. in diameter. The pulmonary orifice, however, was markedly constricted, measuring 8 mm. in diameter. It was partly obstructed by a round structure projecting into the lumen at the usual level of the semilunar valve. This was subsequently identified as an aneurysm of the left aortic sinus, measuring 8 by 5 by 4 mm. and located at the usual site of the right posterior cusp (Fig. 10 and 11). An incision, 5 mm. deep, in the infundibulum (made by the surgeon's instrument) extended through and slightly above this structure which had been thus perforated. No pulmonic cusp could be identified (Fig. 10). An endocardial thickening, possibly a rudimentary cusp, was noted over the anterior wall (Fig. 10 and 12). The pulmonary artery seemed smaller than normal, with a circumference of 2 cm. A high ventricular septal defect measuring 2 cm. in its largest diameter was identified. The pulmonary veins drained into the left atrium and the mitral valve was normal. The left ventricle was dilated, and its walls measured 1 cm. in thickness. The aortic valve annulus measured 2 cm. in diameter. The right and left sinuses of Valsalva were larger than normal (Fig. 13) and the right and left cusps obstructed almost completely the ventricular septal defect (Fig. 10). A slight pressure at the bottom of the sinuses caused the free margin of the left cusp to invert into the left ventricle, suggesting a severe aortic regurgitation during life. A small fenestration of a few millimeters in length was observed at the margin of the right aortic cusp. The left aortic sinus communicated with the aneurysm

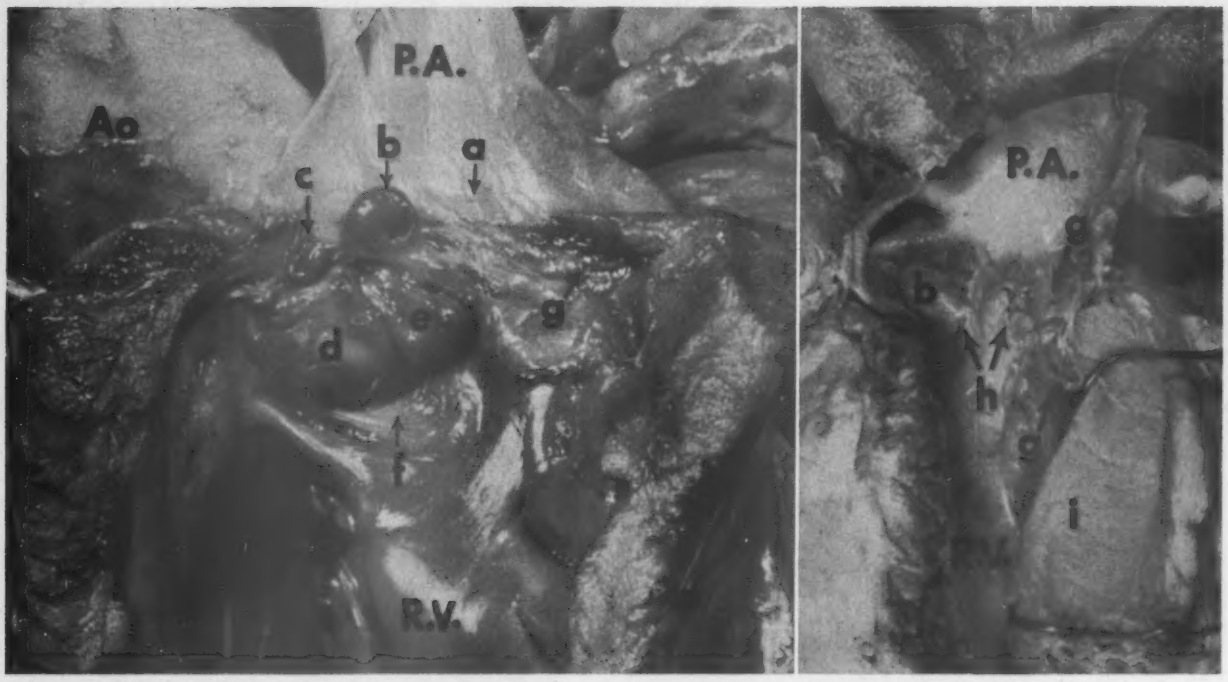

FIG. 10. Case 2. Photographs of the opened pulmonary artery and right ventricle illustrating the following: a, absence of pulmonary cusps; b, aneurysm of the left aortic sinus; c, thickening, possibly a rudimentary cusp; d, right aortic cusp; e, left aortic cusp seen through the ventricular septal defect; f, ventricular septal defect; g, incision made by the surgeon's instrument; h, edges of the sectioned aneurysm (at the site of the incision made by the surgeon); i, section removed for histologic study. P.A. = origin of the pulmonary artery; Ao = aorta; R.V. = right ventricular cavity.

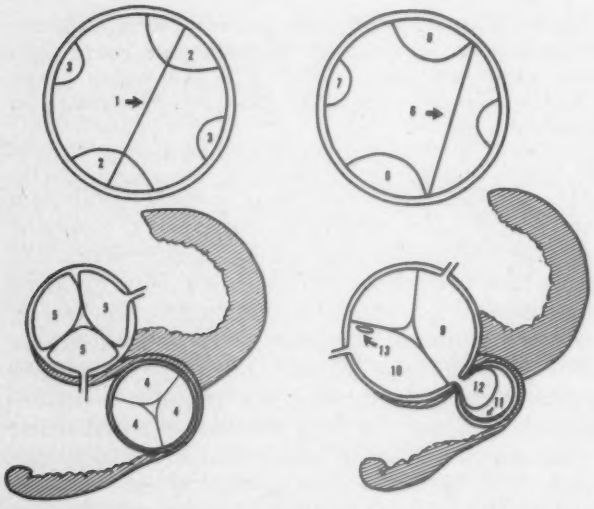

FIG. 11. Diagrams illustrating the formation of the semilunar valves by the partitioning of the truncus arteriosus cummunis. *Left (normal):* The aortopulmonary septum (1) divides the lateral endocardial cushions (2) in two, giving rise with each intercalated valvular swelling (3) to three pulmonic (4) and three aortic (5) cusps. *Right (Case 2):* It is postulated that the septum (6) divided the truncus unequally, including in the aortic trunk the posterior intercalated swelling (7) and the two lateral cushions (8), resulting in three aortic cusps, the left (9) and right (10) of abnormal size, and a single cusp pulmonary valve, rudimentary (11) in this case. (12) Aneurysm of the left aortic sinus; (13) fenestration at the margin of the right aortic cusp.

FIG. 12. Case 2. View of the aortic valve from above, showing the following: a, large right (coronary) sinus; b, large left (coronary) sinus; c, posterior sinus of normal size.

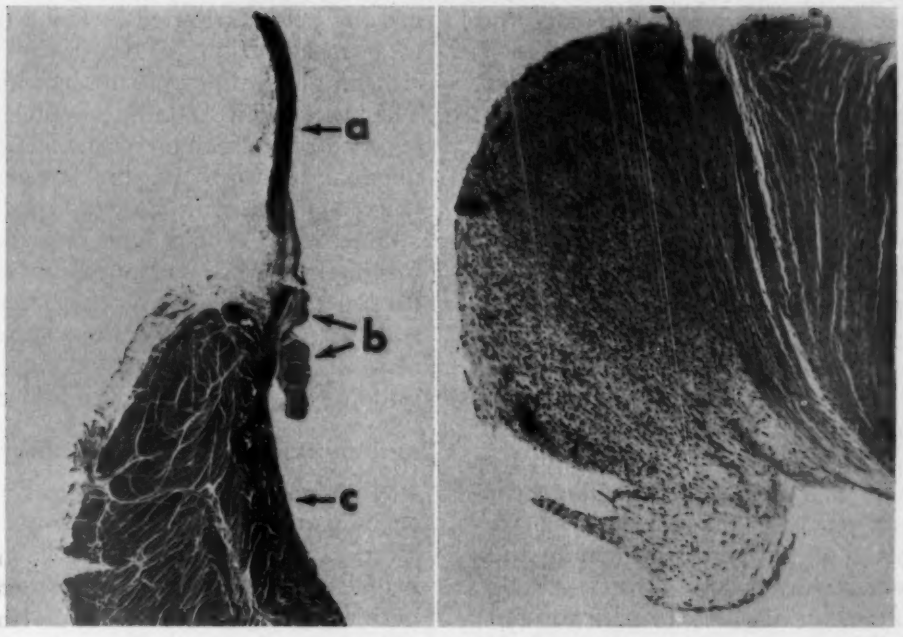

FIG. 13. Case 2. *Left:* Photomacrograph (×4) of a vertical section through the rudimentary cusp at the level of the pulmonic ring showing a, pulmonary artery wall; b, "rudimentary cusp" at the level of the pulmonic ring; c, myocardium. *Right:* Low power magnification (×80) of the "rudimentary cusp" showing dense connective tissue.

previously described at a point near the left-right commissure. The aorta was of normal size but was partially transposed, overriding both ventricles. The remainder of the examination was not remarkable except for a passive congestion of the lungs, liver and brain.

Comments: The diastolic murmur was most likely caused by the pulmonary valve and the aortic valve insufficiency. The aortic valve regurgitation appears to have been significant, as suggested by the wide systemic pulse pressure. The murmur had been described as continuous at times and the possibility of a spontaneous rupture of the aneurysm of the aortic sinus into the right ventricular outflow tract was raised. The absence of a left to right shunt at cardiac catheterization and the anatomic findings previously described have convinced us that the perforation was made by the surgeon's instrument during the transventricular valvotomy. In spite of the constriction of the pulmonic ring or orificial pulmonary stenosis and the obstruction to flow produced by the aortic sinus aneurysm, this patient was not cyanotic. The large aortic cusps partially closed the ventricular septal defect (Fig. 10), but we postulate that the systemic hypertension resulting from the aortic insufficiency prevented a significant right to left shunt. In fact, the right ventricular systolic pressure and systemic systolic pressure (arm cuff) were equal, but the systemic and pulmonary resistances were unfortunately not measured.

COMMENTS

Review of the Literature: Thirteen instances of congenital absence of all pulmonic cusps have been reported,[1–7] of which ten are cases proved at autopsy (Table III). Ehrenhaft[3] discussed the case of a fourteen year old boy in whom an absence of the pulmonary valve was found at surgery. Although he believed that it had been destroyed by subacute bacterial endocarditis or rheumatic fever, it may have been aplastic. There was not postmortem confirmation. Miller and associates[6] described a clinical and pathologic syndrome in six children who presented cyanosis, a to and fro heart murmur, pulsating aneurysmal pulmonary arteries, a bidirectional shunt at the ventricular level and an infundibular pulmonary stenosis. Four of these patients have died and postmortem examination revealed an infundibular pulmonary stenosis, a ventricular septal defect, an overriding aorta and absence of any true pulmonary valve. The other two were presumed to have similar malformations, including the absence of a pulmonary valve.

Pathology and Embryology: This anomaly was associated with a ventricular septal defect in thirteen of the fifteen cases reported thus far, including the two cases described herein. Ehrenhaft's patient[3] was reported to have an isolated absence of the pulmonary valve but no postmortem confirmation was obtained. Case 2 of Smith and associates[7] also had this anomaly as an isolated malformation. In addition to the ventricular septal defect, eight had an infundibular pulmonary stenosis, and all of these except one also had an overriding aorta (tetralogy of Fallot). Three had a constricted pulmonic annulus or an orificial stenosis, but without identifiable valve tissue, a distinction which separates it from a true valvular stenosis. Only two cases[2,4] did not have a pulmonary stenosis of any type in combination with the ventricular septal defect. Finally, one case also had an associated single coronary artery and another, an aneurysm of an aortic sinus of Valsalva (Table III).

The congenital nature of this anomaly is not proved. The absence of histologic evidence of inflammation or destruction, the rarity of acquired pulmonary valvular disease, and the frequent association of other congenital malformations favor this assumption. All these cases had no pulmonary cusp that could be identified as such (Table III). Some had a complete absence of valvular tissue, and others had a thin fold, a fibrous band, smooth or irregular thickenings at the level of the pulmonic ring. Case 2 of Smith et al.[7] had short irregular and fused leaflets, the only case with identifiable leaflets. The histologic studies revealed fibrous tissue,[4,5] avascular loose connective tissue,[7] myxomatous connective tissue (Case 1) and dense connective tissue (Case 2). These considerations suggest that this anomaly in some cases represents an hypoplasia and in others, a true agenesis of some or of all the pulmonic cusps.

Simmonds[8] explained the reduction of pulmonary valve cusps, particularly of bicuspid valves, by a maldirection of the aortic septum, which has improperly divided the endocardial cushions, the precursors of the cusps. Ventricular septal defect, overriding aorta and pulmonary stenosis, anomalies commonly associated with agenesis of the pulmonary valve and with bicuspid pulmonary valve,[9] may also result from an abnormal position of the aortic septum.[10] A single coronary ostium, an anomaly observed in one of the patients with no pulmonary valve,[4] has also been attributed by Roberts and Loube[11] to a misdirection of the aortic septum with crowding together of the coronary anlagen. The association of large aortic cusps with an absence of pulmonary cusps again suggests an unequal division of the truncus arteriosus (Fig. 11). In our Case 2, the anterior pulmonary cusp should have been present if this mechanism were responsible, but the endocardial thickening at that site may represent a rudimentary cusp. The formation of the aneurysm of the aortic sinus, on the other hand, is undoubtedly explained on another basis.

HEMODYNAMIC AND CLINICAL SIGNIFICANCE

Absence of the pulmonary valve is necessarily accompanied by severe pulmonary valve regurgitation. Isolated pulmonary valvular insufficiency appears to be well tolerated in the experimental animal[12–14] and in humans.[15–19] Although significant hemodynamic derangements and cardiac enlargement resulted, congestive failure could not be induced in dogs by complete excision of the pulmonary valve.[12] One of the patients with an isolated complete absence of the pulmonary valve appeared to have been only moderately handicapped.[3] He complained, however, of shortness of breath from four years of age and had a markedly enlarged heart. The other patient[7] with isolated absence of the pulmonary valve was believed to have congestive heart failure *in utero*. This relatively good tolerance in postfetal life may be explained by the low pressure system of the right side of the heart. As suggested by Smith et al.,[7] this anomaly is of greater consequence *in utero* because the pulmonary artery pressures are equal to the systemic pressures and a free communication of the systemic and pulmonary arterial systems through the patent ductus arteriosus results in an aortic run-off into the pulmonary artery, thus increasing the pulmonic regurgitation. We presume that when pulmonary hypertension or a large left to right shunt is added, the regurgitation is similarly increased and the right ventricular overload may be less well tolerated. However, the two patients with a large associated ventricular septal defect became significantly incapacitated only during the last few years, and they lived to the age of thirty-two and forty-six years, respectively.[2,4] On the other hand, an associated pulmonary stenosis may minimize this regurgitation by reducing the pulmonary blood flow.

TABLE III

Reported Cases of Absence of Pulmonary Valve. Associated Malformations

Authors	Sex and Age (years)	Findings at Site of Pulmonary Valve	Right Ventricle Infundibulum	Pulmonic Ring	Pulmonary Artery	Ventricular Septum	Aorta	Other Structures
Roger and Wilson[1]	M, 6 1/2	Absence of valve	Localized stenosis (?)	Constricted (3–8 mm.)	Small	High defect (1.5 cm.)	Transposed	Transposed atria (situs inversus); atrial septal defect, mitral hypoplasia and atrophic left ventricle
Lavennes et al.[2]	M, 46	Thin fold of tissue	Thin fold over posterior third, without true stenosis	...	Dilated	High defect (1.8–0.8 cm.)	Overriding	Small fenestration of the noncoronary aortic cusp
Ehrenhaft[3]*	M, 14	No leaflets	...	...	Dilated	...	...	
Campeau et al.[4]	M, 32	Fibrous rim 2 cm. in length	No stenosis	Not constricted	Aneurysmal	High defect (2.5 cm.)	Small	Single coronary artery
Onesti and Harned[5]	M, 9 weeks	Small irregular thickenings of fibrous tissue	No stenosis	Mild constriction (1.5 cm. circumference)	Dilated	High defect	Overriding	Patent foramen ovale
Miller et al.[6]	Children (6 cases)†	Absence of valve	Stenosis	...	Dilated	Defect	Overriding	
Smith et al.[7]	M, 4 1/2	No valvular tissue	Moderate stenosis	Mild constriction	Dilated	High defect	Normal	
	M, premature	Irregular, short and adherent leaflets	Normal	Normal	Dilated	Normal	Small	Patent foramen ovale and ductus arteriosus
Case 1	M, 1 1/4	Two small excrescences, smooth thickenings	Localized stenosis	No constriction	Dilated	High defect (1 cm.)	Overriding	
Case 2	F, 7	Single "rudimentary cusp," aneurysm of aortic sinus	Normal	Constricted (2.3 cm. circumference)	Smaller than normal	High defect (2 cm.)	Overriding	"Aneurysmal" dilatation of two aortic sinuses of Valsalva

* Direct surgery observation. No autopsy.

† Two cases without autopsy confirmation.

The diagnosis of isolated organic pulmonary valve regurgitation has been recently reviewed.[15–20] A short gap between the pulmonic second heart sound and the onset of the diastolic murmur is frequently observed. A systolic click is not infrequent. Of interest is the finding of a diastolic thrill and rumble over the tricuspid or the mitral area, which according to Segel et al.[18] may be the equivalent of the Austin Flint murmur of aortic regurgitation. The electrocardiogram usually shows a right ventricular diastolic overload pattern or right bundle branch block with or without right ventricular hypertrophy. At fluoroscopy, the pulmonary arteries are dilated and abnormally pulsatile, falsely suggesting a left to right shunt. At cardiac catheterization, the pulmonary artery pressure curve may suggest the diagnosis. The most significant findings are a diastolic pressure approaching the right ventricular end diastolic pressure and a less prevalent or absent incisura. The pulmonary artery and right ventricular pressure patterns become almost similar in cases of severe regurgitation. Segel and associates[18] described an early systolic negative wave believed to be a Venturi effect and not unlike the pattern observed by Wiggers in aortic insufficiency. A pressure gradient of 10 to 30 mm. Hg may also be observed due to an increased flow through the pulmonic orifice. More recently, diagnostic methods with the aid of dye dilution technics[20] and angiocardiography[21] have been described.

Clinical Findings: Loud systolic and diastolic murmurs over the left side of the sternum were described in all cases of absence of the pulmonary valve, except in Case 2 of Smith and associates (auscultatory findings not given). The systolic murmur was due to associated anomalies except in Ehrenhaft's case in which no other malformation was described. The pulmonic second sound was inaudible[3,4,5,7] (our Case 2), or a single second sound was heard over the pulmonic area[2] (our Case 1). This single second sound was noted in patients with an overriding aorta and was presumably transmitted from the aortic valve because of the abnormal position of the aortic orifice. The second pulmonic sound was not mentioned by Roger and Wilson[1] and by Miller[6] and associates in the description of their cases. The pulmonary artery was markedly dilated and pulsatile in all cases except in two[1] (our Case 2). These two patients had severe constriction of the pulmonary orifice but the patients with infundibular stenosis had these findings as well.

A right bundle branch block or an rsR′ pattern in V_1-V_2 in addition to the right ventricular hypertrophy was reported in five[3,4,7] of the seven cases with a description of the electrocardiogram (two cases reported herein). The patients of Lavennes and associates[2] and of Onesti and Harned[5] had a qR in V_1 but an rsR′ in V_2, which can possibly be interpreted as right bundle branch block with right atrial and right ventricular hypertrophy.[22] This bundle branch block is probably due to the right ventricular diastolic overload resulting from the pulmonary valve regurgitation.

The pulmonary artery pressure was described in only three cases. Ehrenhaft's[3] patient had a pulmonary artery pressure of 27/10 mm. Hg with a right ventricular pressure of 50/7 mm. Hg. Another case[4] had a pulmonary artery pressure of 180/23-28 with a right ventricular pressure of 180/0 mm. Hg. Finally the patient described by Smith et al.[7] had a pulmonary artery pressure of 44/33 with a right ventricular pressure of 75/2 mm. Hg. None of these cases, except possibly Ehrenhaft's case, had a pulmonary artery diastolic pressure equal to or approaching right ventricular diastolic pressure, a "pathognomonic" sign of pulmonary valve regurgitation. No explanation can be offered for this discrepancy. In our Case 1, none of the previously described signs of pulmonary valve regurgitation were observed (Fig. 3), whereas in Case 2, the pulmonary artery diastolic pressure was equal to the right ventricular end diastolic pressure (Fig. 9).

Combined Absence of Pulmonary Valve and Tetralogy of Fallot: Absence of the pulmonary valve confuses the diagnosis of the anomalies with which it is associated, and which are usually recognized otherwise without difficulty, such as the tetralogy of Fallot. We suggest, as do Miller et al.[6] that the combination of this anomaly and the malformations of the tetralogy of Fallot results in a characteristic clinical syndrome. Cyanosis, systolic and diastolic murmurs, an aneurysmal pulmonary artery, a right ventricular-pulmonary artery pressure gradient, and a bi-directional shunt at the ventricular level were observed in the six cases of Miller et al., in Case 1 of Smith et al.[7] and in our Case 1. Smith and associates' patient, however, had cyanosis only in early infancy and the murmur was described as continuous instead of "to and fro." This was the only case without an overriding aorta. We add to the description of Miller

and associates,[6] partial right bundle branch block associated with right ventricular hypertrophy, which is rarely observed in a true tetralogy of Fallot. Not a single case of right bundle branch block has been found in a series of sixty-three cases of tetralogy of Fallot[23] and we have observed an rsR′ pattern in V_1 or in V_2 in only two tracings of fifty patients with a diagnosis of tetralogy of Fallot. Of these two patients, one had an associated bicuspid pulmonary valve and the other had pulmonary fibrosis due to healed tuberculosis. The presence of a normal or loud single second sound at the pulmonic area should not rule out pulmonary regurgitation, because in tetralogy of Fallot the aortic valve closure sound is usually heard over the second left intercostal space.

Organic pulmonary valve regurgitation could have been suspected in our Case 1 and dye dilution with a double lumen catheter or a selective pulmonary artery angiogram would have certainly detected it. In our Case 2, on the other hand, the associated aortic valve regurgitation was sufficient to explain the diastolic murmur. The degree and significance of the pulmonary valve insufficiency in Case 2 is difficult to evaluate in the presence of these multiple associated malformations. It may have been responsible for the incomplete bundle branch block but it was probably otherwise of little consequence in comparison to the orificial pulmonary stenosis and the aortic valve anomalies.

Summary

Two case reports of congenital absence of the pulmonary valve are presented. In one, associated ventricular septal defect, overriding aorta and an infundibular pulmonary stenosis were observed. In the other, aneurysm of the left aortic sinus and a dilatation of both coronary sinuses of Valsalva were found in addition to a ventricular septal defect, overriding aorta and an orificial pulmonary stenosis.

Thirteen other instances of this anomaly have been previously reported and it was most frequently associated with a ventricular septal defect and pulmonary stenosis (tetralogy of Fallot). This anomaly is accompanied by clinical signs of organic pulmonary valve insufficiency. The combination of absence of the pulmonary valve with the malformations of the tetralogy of Fallot is believed to result in a distinct clinical syndrome, manifested by cyanosis, systolic and diastolic murmurs, aneurysmal pulmonary artery, a right ventricular-pulmonary arterial pressure gradient, and a bidirectional shunt at the ventricular level.

It is suggested that the combination of absence of the pulmonary cusps and abnormally large aortic cusps favors the hypothesis of an unequal division of the truncus arteriosus as the embryologic error responsible for the reduction of pulmonary cusps in some cases.

Acknowledgment

We acknowledge, with appreciation, the criticisms of Dr. Paul David, Director of the Institute of Cardiology. We are indebted to Dr. Osman Gialloreto, Chief of the Hemodynamic Laboratory, to Dr. Louis Philip Legresley, Chief of the Pathology Department, and to Dr. Jules Laberge, Chief of the Radiology Department, Institute of Cardiology and Maisonneuve Hospital. We also thank Mr. Jean Gauthier and Miss Jacqueline Dupuis of the Medical Illustration Department for their collaboration.

References

1. Roger, B. F. and Wilson, J. D. Incomplete heterotaxy with unusual heart malformations. Case report. *Arch. Pediat.*, 25: 881, 1908.
2. Lavennes, F., Tyberghein, J., Brasseur, L. and Meersseman, F. Complexe d'Eisenmenger avec insuffisance pulmonaire par absence de valvules. *Acta cardiol.*, 9: 249, 1954.
3. Ehrenhaft, J. L. Discussion of paper by Ellison et al.[13]
4. Campeau, L. A., Ruble, P. E. and Cooksey, W. B. Congenital absence of pulmonary valve. *Circulation*, 15: 397, 1957.
5. Onesti, S. J., Jr. and Harned, H. S., Jr. Absence of pulmonary valve associated with ventricular septal defect. *Am. J. Cardiol.*, 2: 496, 1958.
6. Miller, R. A., White, H. and Lev, M. Congenital absence of the pulmonary valve: clinical and pathological syndrome. *Circulation*, 18: 759, 1958.
7. Smith, R. D., DuShane, J. W. and Edwards, J. E. Congenital insufficiency of the pulmonary valve. *Circulation*, 20: 554, 1959.
8. Simmonds, J. P. Congenital malformations of the aortic and pulmonary valves. *Am. J. M. Sc.*, 166: 584, 1923.
9. Edwards, J. E. Congenital malformations of the valve. In: Pathology of the Heart, 2nd edition, p. 407. Edited by Gould, G. E. Springfield, Illinois, 1959. Charles C Thomas.
10. Kramer, T. C. The partitioning of the truncus and conus and the formation of the membranous portion of the interventricular septum in the human heart. *Am. J. Anat.*, 71: 343, 1942.
11. Roberts, J. T. and Loube, S. D. Congenital single coronary artery in man. *Am. Heart J.*, 34: 188, 1947.
12. Barger, A. C., Roe, B. B. and Richardson, G. S. Relation of valvular lesions and exercise to auricular pressure, work tolerance and to development of chronic congestive failure in dogs. *Am. J. Physiol.*, 169: 384, 1952.
13. Ellison, R. G., Brown, W. J., Jr., Hague, E. E. and Hamilton, W. F. Physiological observa-

tions in experimental pulmonary insufficiency. *J. Thoracic Surg.*, 30: 633, 1955.

14. Reffe, J. W., Hart, R. L., Belmonte, Batcli. and Gerbrode, F. The physiological effects of experimental total pulmonary insufficiency. *Surgery*, 41: 43, 1957.
15. Giraud, G., Latour, H. and Puech, P. Etude anatomique d'une insuffisance pulmonaire sigmoidienne congénitale confrontée avec les données cliniques et hémodynamiques anteriéurement recueillies. *Montpellier med.*, 44: 544, 1953.
16. Kohout, F. W. and Katz, L. N. Pulmonic valvular regurgitation. Report of a case with catheterization data. *Am. Heart J.*, 49: 637, 1955.
17. Ford, A. B., Hellerstein, H. K., Wood, C. and Kelly, H. B. Isolated congenital bicuspid pulmonary valve. *Am. J. Med.*, 20: 479, 1956.
18. Segel, N., Venlingen, B., Resnekov, V. and McGregor, H. Isolated congenital pulmonary incompetence. *South African M. J.*, 31: 1157, 1957.
19. Lendrum, B. L. and Shaffer, A. B. Isolated congenital pulmonic valvular regurgitation. *Am. Heart J.*, 57: 298, 1959.
20. Bajec, D. F., Birkhead, N. C., Carter, S. A. and Wood, E. H. Localization and estimation of severity of regurgitant flow at the pulmonary and tricuspid valves. *Proc. Staff Meet. Mayo Clin.*, 33: 569, 1958.
21. Collins, N. P., Braunwald, E. and Morrow, A. G. Isolated congenital pulmonic valvular regurgitation. Diagnosis by cardiac catheterization and angiocardiography. *Am. J. Med.*, 28: 159, 1960.
22. Sodi-Pallares, D. and Calder, R. M. New Bases of Electrocardiography, pp. 236, 287. St. Louis, 1956. The C. V. Mosby Co.
23. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease, 2nd Edition, p. 255. Chicago, 1959. The Year Book Publishers.

Rupture of the Aortic Valve Due to Strain*

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THE clinical picture of rupture of the aortic valve secondary to strain or trauma has been recognized for many years. Only in recent years has it been possible to attempt the surgical correction of such lesions. Recently we have had the opportunity to observe a patient with rupture of the aortic valve following strain. Surgical repair of the defect was attempted. Even though this patient did not survive the procedure, the case is being reported since surgical intervention seems to offer the only chance to halt an otherwise progressive and eventually fatal course.

CASE REPORT

A sixty-two year old farm laborer (No. 17-08-30) suddenly had an episode of severe substernal pain radiating to the left scapula and down the left side of his back on October 10, 1959, while carrying a 25 pound block of ice. The pain subsided after a few minutes. The patient then developed progressive shortness of breath and subsequently coughed up frothy pink sputum. A physician treated the patient with digitalis and diuretics without definite improvement. The patient was referred to the University of Arkansas Medical Center on October 20, 1959 to be evaluated for a possible ruptured aortic cusp.

The patient stated that he had been in excellent health all his life except for gonorrhea in 1912 and influenza in 1918. The patient specifically denied any history of syphilis or rheumatic fever. A physician had told him in 1955 that he had hypertension.

On admission his blood pressure was 150/50 mm. Hg in the right arm. The pulse was 100 per minute and regular. The respirations were 26 per minute and he weighed 126 pounds. The temperature was 98.4° F. His vital capacity was 2.6 L. with a rapid flow. The patient appeared dyspneic but was in no acute distress. Funduscopic examination revealed arteriolar narrowing and A-V nicking. In the supine position the neck veins were distended and filled from below. There was an exaggerated pulsation of both carotid arteries. Dullness and decreased breath sounds were present over both lung bases. Examination of the heart revealed the point of maximal impulse 3 cm. lateral to the left midclavicular line in the sixth intercostal space. The rhythm was regular. A middiastolic thrill was palpable at the apex. Over the base a grade 2 systolic murmur, followed by an accentuated second aortic sound and a grade 3 high-pitched diastolic decrescendo murmur, were heard. A low-pitched rumbling grade 3 middiastolic murmur was audible over the apex. The liver edge was palpated 7 cm. below the right costal margin. The peripheral pulses were equal in both arms and had a water hammer quality. Duroziez' sign was elicited over the femoral arteries. There was slight bilateral pretibial edema.

Urinalysis revealed no abnormalities. The hemoglobin was 11.2 gm. per cent and the hematocrit was 35 per cent. A serologic test for syphilis (VDRL) was negative. The blood urea nitrogen was 23 mg. per cent. The venous pressure was equivalent to 120 mm. of saline with rise to 230 mm. on pressure over the liver. The circulation time (Decholin,® arm to tongue) was nineteen seconds.

Roentgenograms of the chest showed congested lung fields and bilateral pleural effusion. The aortic shadow did not appear enlarged. The heart was enlarged, predominantly in the region of the left ventricle (Fig. 1).

An electrocardiogram revealed a sinus mechanism with a rate of 90 per minute and changes suggestive of left ventricular hypertrophy and digitalis effect (Fig. 2). There was no evidence of a recent or remote myocardial infarction.

Course: On a regimen consisting of restricted activity, limited sodium intake and digitalis, the patient lost 17 pounds in the next twelve days with considerable subjective and objective improvement. The patient was then discharged from the hospital with the clinical diagnosis of a ruptured aortic cusp. He became progressively short of breath despite strict adherence to his cardiac regimen. The venous pressure on a clinic visit on January 4, 1960 was equivalent to 180 mm. of saline with rise to 250 mm. on hepatic pressure. His circulation time (arm to tongue) was thirty-four seconds. The patient was readmitted to the hospital on January 11, 1960. The cardiac findings were unchanged. He again made some improvement on a strict cardiac regimen. *A*

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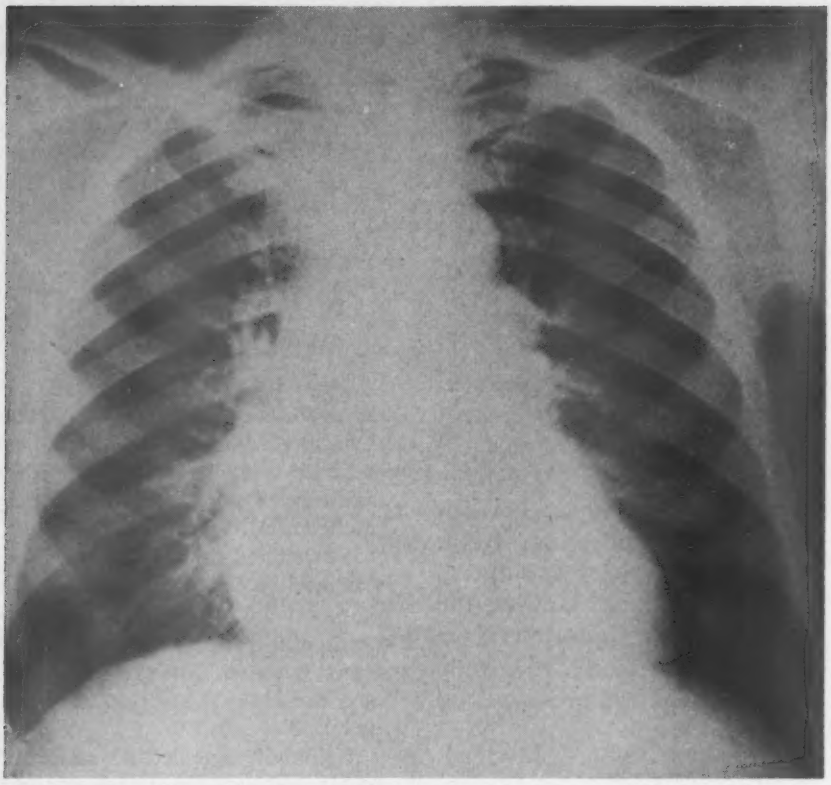

FIG. 1. Chest film which shows enlargement of the left ventricle and pulmonary congestion.

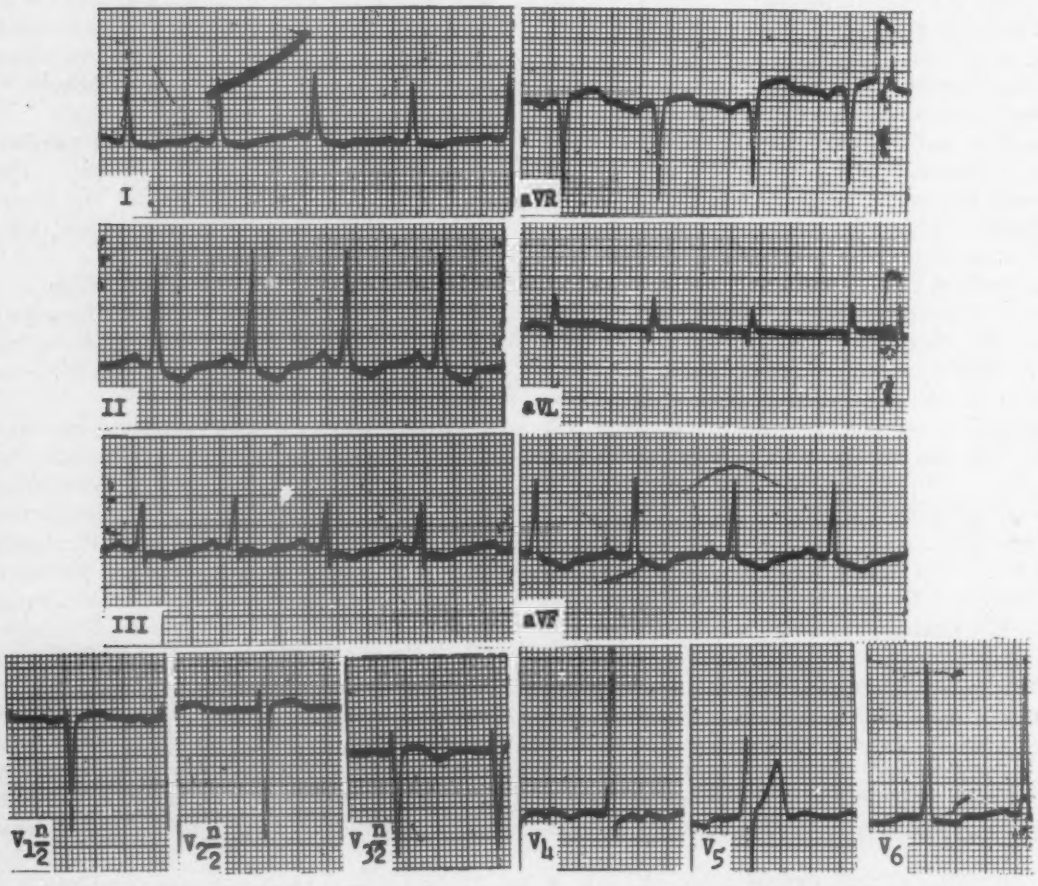

FIG. 2. Electrocardiogram exhibiting left ventricular hypertrophy and digitalis effect.

FIG. 3. Retrograde aortogram which reveals reflux of dye into the left ventricle indicating aortic valvular incompetency.

retrograde aortogram (Fig. 3) showed reflux of dye from the aorta into the left ventricle. No evidence of a dissecting or localized aneurysm was seen.

Surgical Findings and Results: On January 26, 1960 an attempt was made to repair the valvular defect using a Kay-Cross pump-oxygenator. The ascending aorta was dilated, measuring 6 cm. in diameter, but free of any inflammatory reaction suggestive of a recent dissecting aneurysm. A diastolic thrill was present in the left ventricle. Extracorporeal perfusion was instituted at an estimated flow rate of 62 cc./kg./minute. This maintained the arterial pressure in the range of 75 to 105 mm. Hg. In the initial eight minutes of the bypass procedure the venous return exceeded the arterial output by approximately 2,300 cc. of blood. A longitudinal J-shaped incision was made in the base of the aorta revealing a linear rent 6 mm. long in the anterior half of the left posterior aortic leaflet running parallel and about 1.5 mm. medial to the annulus (Fig. 4). The tear crossed the free edge of the leaflet near the commissure and extended proximally and anteriorly for a distance of 6 mm. in an oblique direction through the intima of the aorta. The leaflets were slightly thickened but otherwise normal in appearance and seemed to close adequately after the rent had been repaired with several No. 4-0 arterial silk sutures. The aorta was partly sutured after which the rest of the opening was occluded by a Satinsky clamp and the aortic clamp released to permit perfusion of the coronary arterial bed. The heart began to beat strongly within a period of two to three minutes.

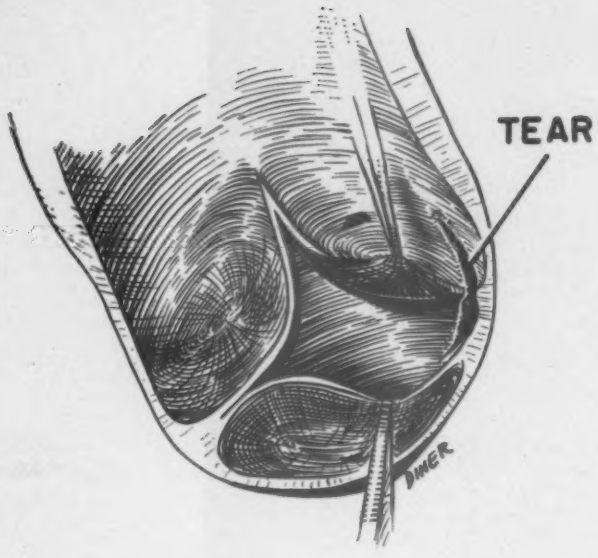

FIG. 4. Drawing illustrating tear in the anterior portion of the left coronary cusp.

The procedure had taken about fifteen minutes to this point but complete extracorporeal perfusion was continued for an additional ten to twelve minutes to permit the heart to recover from the effects of ischemic arrest with decompression of the chambers being achieved through vents previously placed in both atria. The remainder of the aortotomy was sutured during this time. The cardiac action appeared strong and the atrial vents were occluded and partial cardiac bypass instituted. A brief period of bypass was reinstituted to facilitate closure of a small leak in the posterior aspect of the aortotomy when it was observed that the heart had ceased beating and that the arterial and venous blood was exceedingly dark. A hasty check revealed that the oxygen inlet tube had become obstructed. Oxygen was introduced directly into the oxygenating chamber and extracorporeal perfusion continued for another thirty minutes in an attempt to resuscitate the heart. Despite adequate perfusion of the coronary arteries and repeated attempts at defibrillation, the heart could not be permanently revived.

COMMENTS

Cases of rupture of the aortic valve due to strain or trauma have been reported sporadically for over one hundred years. In 1925 Howard reviewed the data of 112 cases reported from 1830 to 1925 and added another case of his own.[1] The diagnosis was proved by autopsy in forty-eight cases.

In sixty cases rupture was considered to be due to muscular strain and in the remaining cases secondary to trauma or unstated causes. All except one of the cases due to strain had occurred in men whose ages ranged from twenty to sixty years with an increased incidence in the fourth and fifth decades. Usually only one cusp was affected, most commonly the anterior leaflet, but involvement of two cusps was reported occasionally. At autopsy the valve was considered to be otherwise "normal" in only seven, or 23 per cent of the cases. The majority of the protocols described the valve as thickened, atheromatous or even calcareous.

The most common initial symptom is severe pain within the chest occurring during physical exertion. The pain is described as acute and agonizing and may be associated with a sudden tearing sensation within the chest. It is primarily in the precordium or epigastrium and usually radiates to the neck and left shoulder and sometimes into the back between the shoulder blades. The patient may become immediately conscious of a "roaring or buzzing sensation" in his chest. Dyspnea occurs usually immediately after the accident. The clinical picture is characterized by the suddenness of the onset of symptoms in a previously healthy subject and the rapid development of progressive intractable heart failure together with the circulatory signs of free aortic regurgitation. The musical quality of the aortic diastolic murmur has been repeatedly emphasized. Several authors, however, have detected murmurs of this character more commonly in aortic insufficiency secondary to syphilis or bacterial endocarditis.[2,3]

The prognosis will vary with the size of the tear and the degree of valvular insufficiency produced. In the great majority of reported cases the clinical course has been one of rapidly progressing cardiac failure with death occurring within months.

Because of the poor prognosis Bean and Schmidt[4] questioned in 1953 the value of discovering rupture of the aortic valve during life, other than for the enhancement of the clinician's pride in his diagnostic astuteness. Bean also suggested that this injury represented an ideal situation for surgical intervention. Leonard, Harvey and Hufnagel[5] in 1955 were able to report such an attempt in a seventeen year old boy (with traumatic rupture of the aortic valve). They inserted a plastic valve into the descending aorta. Even though the clinical picture was complicated by a left to right shunt at the ventricular level, the patient was asymptomatic and doing heavy labor fourteen months

after surgery. Dimond et al.[6] reported a case of post-traumatic aortic insufficiency in a patient with Marfan's syndrome in whom surgical repair was unsuccessfully attempted. It would seem that surgical intervention should be attempted as early as possible in this disorder since otherwise the prognosis is extremely grave.

Summary

A case of rupture of the aortic valve due to physical strain is presented. Surgical repair of the defect utilizing a cardiac bypass procedure was attempted but was unsuccessful. A short discussion of the clinical picture of this disorder is added and emphasizes the necessity for attempted repair of this defect to avoid the usual rapidly progressing cardiac failure and death.

References

1. Howard, C. P. Aortic insufficiency due to rupture by strain of a normal aortic valve. *Canad. M.A.J.*, 19: 12, 1928.
2. Gelfand, D. and Bellet, S. The musical murmur of aortic insufficiency; clinical manifestations; based on a study of 18 cases. *Am. J. M. Sc.*, 221: 644, 1951.
3. Stembridge, V. A., Hejtmancik, M. R. and Herrmann, G. R. Unusual musical murmurs of anterior cusp aortic regurgitation. *Am. Heart J.*, 48: 163, 1954.
4. Bean, W. B. and Schmidt, M. C. Rupture of the aortic valve: disappearing diastolic pressure as diagnostic sign. *J.A.M.A.*, 153: 214, 1953.
5. Leonard, J. J., Harvey, W. P. and Hufnagel, C. A. Rupture of the aortic valve: a therapeutic approach. *New England J. Med.*, 252: 208, 1955.
6. Dimond, E. G., Larsen, W. E., Johnson, W. B. and Kittle, C. F. Post-traumatic aortic insufficiency occurring in Marfan's syndrome, with attempted repair with a plastic valve. *New England J. Med.*, 256: 8, 1957.

Aberrant Origin of Left Coronary Artery Combined with Mitral Regurgitation in an Adult*

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THE PURPOSE of this report is to record a case with an abnormal origin of a coronary artery from the pulmonary artery, combined with mitral regurgitation.

Anomalous origin of the coronary arteries is a rare congenital abnormality. Less than seventy-five cases have been reported in the world literature.[1-6] Because of a developmental defect in the embryonic division of the common arterial trunk, the left coronary artery originates from the pulmonary artery rather than from the aorta. In rare cases, the right or even both coronary arteries may originate from the pulmonary trunk.

Bland, White and Garland[7] were the first to describe the clinical syndrome. Symptoms usually occur between the second and sixth month of life and death ensues before one year of age. Some of the cases were symptom-free and the abnormality was noted at autopsy when these infants died from other causes. Fifteen patients survived to adult life,[3,4] the highest age being sixty years and the lowest, sixteen;[5] only one published case so far has provided clinical evidence of associated mitral regurgitation.[3]

CASE REPORT

M. J., a twenty-six year old white woman,* was admitted on June 21, 1959, with a four-month history of dyspnea on exertion and edema of the ankles. The detailed history from the referring physician was as follows:

The patient is now twenty-six years old, married and has no children. She is a nonidentical twin, her sister being entirely healthy. She is said to have been born with a heart murmur. She developed normally and participated in all activities in school, although she fainted about eight times, most episodes lasting about one minute, except the last two bouts, which may have lasted five to ten minutes. Each syncopal attack occurred on physical exertion. She never had convulsions but twice had fecal and urinary incontinence with the attacks.

For years she had noted mild exertional dyspnea on rapid walking and on climbing stairs, usually associated with pounding of the heart. She has had a great many infections of the upper respiratory tract throughout her childhood and in adolescence, usually associated with bronchitis.

In 1957 she was married, and went skiing for two seasons at 7,000 feet altitude without difficulty. The patient gave no history suggestive of rheumatic fever.

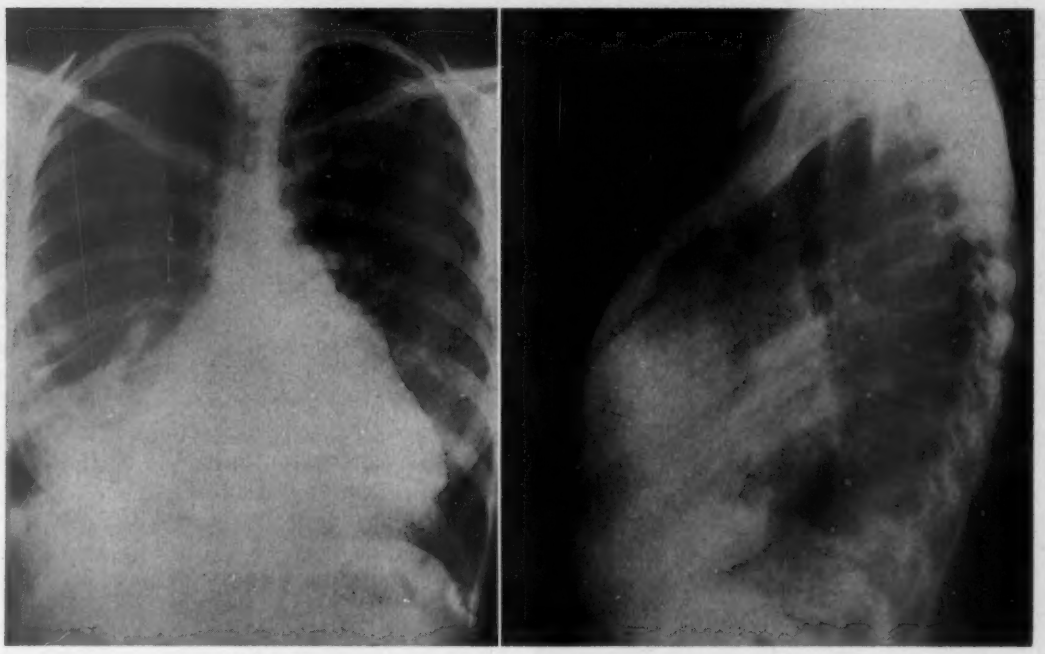
In April 1958 she had her first episode of paroxysmal atrial fibrillation which converted promptly to sinus rhythm after the administration of quinidine and digitalis. She later discontinued the quinidine but continued taking the digitalis.

In March 1959, she was three months pregnant and suffered from recurrent atrial fibrillation. Quinidine on an outpatient basis did not control the fibrillation and before further measures were taken the patient had a miscarriage on March 17, 1959. On March 30, 1959 she came to the office in severe congestive failure. She was hospitalized and the failure was fairly easily controlled with the usual measures of salt restriction and diuretics. Strenuous attempts at conversion of atrial fibrillation were unsuccessful. Since discharge from the hospital on April 4, 1959 the patient has been in failure every time she has been seen in the office.

Pertinent Physical Findings: The patient was a moderately developed woman in no acute distress. The neck veins were not distended. A few râles

* Patient referred by Dr. R. Lenel, Permanente Medical Group, Oakland, California.

* From the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.



A B

FIG. 1. A and B. Roentgenogram of the chest demonstrating evidence for hypertrophy of both ventricles in addition to left atrial dilatation. Vascular markings were accentuated within both lung fields.

were audible at the lung bases. The cardiac impulse was prominent in the fifth left intercostal space in the midclavicular line and an apical systolic thrill was present. A grade 4 harsh apical systolic murmur was present which was transmitted far into the back with a peculiar resonant component in the axilla. The murmur varied with respiration and position. The mitral first sound was very loud. No presystolic or diastolic murmur was heard. There was a distinct third heart sound. Pulmonic second sound was markedly accentuated.

Laboratory Findings: The routine laboratory tests, including blood studies and serum electrolytes, were within normal limits. X-ray examination of the chest and fluoroscopy (Fig. 1A) revealed increased pulmonary vascular markings, but no hilar dance. The heart was markedly enlarged with probable hypertrophy of both ventricles and diiatation of the left atrium (Fig. 1B).

Circulation time (arm to tongue) was twenty-eight seconds with Decholin.

The electrocardiogram (Fig. 2) showed the presence of atrial fibrillation with a well-controlled ventricular response. Left ventricular hypertrophy was present. Small R waves were noted to the right of the precordium.

Hospital Course and Surgical Findings: The patient responded to treatment with bed rest, salt restriction, digitalis and diuretics. As this patient was thought to be a clear-cut case of severe mitral insufficiency, dye studies and cardiac catheterization studies were not performed. Over a period of two weeks she was

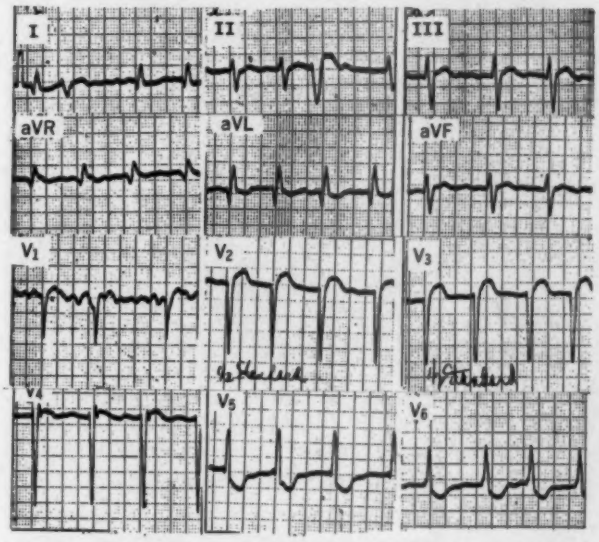


FIG. 2. Electrocardiogram demonstrating evidence for atrial fibrillation and left ventricular hypertrophy. The initial upward deflection in V_1 through V_4 were of small amplitude.

gradually prepared for surgery to repair the mitral insufficiency.

On July 10, 1959 plication of the mitral valve annulus was done, using an open heart technic. The mitral valve was incompetent posteriorly and there was minimum deposit of calcium in back of the two fibrotic cusps. There were dense adhesions in the precordium prohibiting proper inspection of the

FIG. 3. A, left coronary artery arising from the pulmonary artery. B, right coronary artery arising from the aorta. Note fibroelastosis of the left ventricle beneath the valve ring. C, mitral valve.

coronary vessels. A satisfactory correction of the valvular deformity was accomplished and the regurgitation eliminated.

Postoperatively, the patient was well for five hours, when ventricular tachycardia and cardiac arrest suddenly developed. She was revived by manual systole but later went into deep coma and died.

POSTMORTEM FINDINGS

Macroscopic Findings: The heart weighed 550 gm. The pericardium was thickened and the pericardial space was obliterated. On opening the pulmonary artery, no thrombus was found. The epicardium was

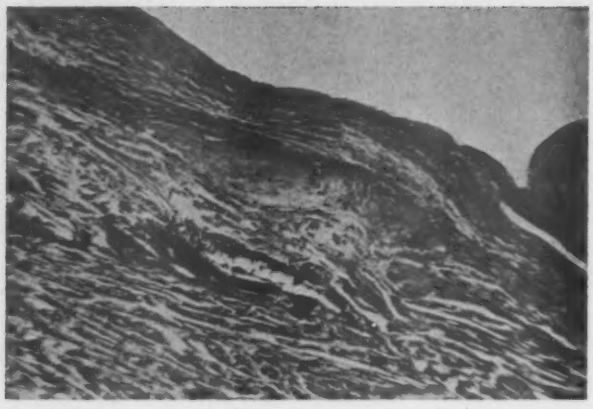


FIG. 4. Microscopic section specially stained to demonstrate the predominance of elastic tissue in the endocardium.

rough and hemorrhagic with many fibrinous adhesive bands attached to it. The endocardium over the whole of the left ventricle was markedly thickened and yellow in color. In some areas there was focal calcification. The chordae tendineae were not markedly thickened. The mitral valve was calcific and posteriorly there were black silk sutures in the annulus fibrosus. The remaining valves were thin and appeared competent. The myocardium of the right ventricle was 1 cm. in thickness and that of the left ventricle was 1.8 cm. The coronary arteries were abnormal in size and distribution. The thick, tortuous right coronary artery arose from the aorta. The left coronary artery arose from the pulmonary artery (Fig. 3). It was thin and veinlike in appearance. There was a well developed anastomosis between the two coronary arteries over the myocardium of the left ventricle. Both coronary arteries were patent and were normal in the rest of their course.

Microscopic Examination: There was complete loss of architecture in the myocardium due to focal areas of fibrosis. The endocardium was markedly thickened and fibrotic and showed elastic fibers by special stains (Fig. 4). In areas, the fibrosis extended into the deeper layers. The epicardium appeared edematous and there was some fibrinoid degeneration seen with formation of granulation tissue. The myocardium was very thin at the apex.

COMMENTS

According to Kaunitz[8] the greater incidence of anomalous origin of the left coronary artery as compared with the right may be explained by the proximity of the sinus of Valsalva of the aorta to the septum of the truncus arteriosus with the result that a small displacement of its angle would cause the left coronary ostium to fall within the pulmonary artery.

The syndrome affects women roughly twice as often as men.[1,2,6]

Electrocardiographic changes are characteristic of myocardial ischemia. There is generally a tendency towards left axis deviation and in 50 per cent of the cases, left ventricular hypertrophy.[9,10]

Hemodynamics: Normally, the oxygen content of the arterial blood (aorta and coronary arteries) is 19 volumes per cent. The arteriovenous oxygen difference in the coronary circulation approximates 15 volumes per cent; therefore, it is apparent that the cardiac musculature extracts nearly all of the oxygen that is delivered to it. Partial perfusion of the ventricles with venous blood with an oxygen content ranging from 12 to 14 volumes per cent can only lead to an oxygen debt with interference in cardiac performance. In the asymptomatic neonatal phase the high pressure in the pulmonary artery and patency of the ductus arteriosus probably help to maintain a reasonably adequate coronary blood flow.[5] Later, however, the fall in the pulmonary artery pressure and increasing work load of the left ventricle result in anoxia and myocardial damage. The secondary stasis further decreases the pulmonary and left coronary flow and a vicious cycle is established.

In the adult cases of aberrant left coronary artery, the left ventricular lesions have been less marked than in infancy, or even absent. The left coronary artery has usually been dilated and thin walled, resembling a vein. The right coronary artery has been markedly dilated, tortuous and cirsoid with an extensive collateral circulation. Coronary atherosclerosis, when present, has involved only the right coronary artery.[5]

The additional burden imposed by mitral regurgitation (congenital or acquired) increases the oxygen and nutritional requirements of the left ventricle, accelerating the development of left ventricular hypertrophy. The pathologic changes described previously represent the end stages of chronic hypoxia because of partial perfusion of the heart with venous blood and interference with coronary perfusion as a result of a diminution in effective cardiac output.

Anomalous Coronary Arteries and Mitral Insufficiency: Several anomalies of the coronary arteries have been described.[11] Arteriovenous aneurysms of varying sizes are the most common. Only one case has been reported so far in which there was an associated mitral insufficiency and the cause has been described as rheumatic valvulitis.[8]

Edwards quotes Roberts and Loube:[12] "It is well to emphasize that a congenitally single coronary artery is capable of supplying adequately the entire heart, unless by chance it becomes the site of acquired disease."

Anomalous left coronary artery presents the features of an A-V shunt plus insufficient perfusion of the left ventricle because of low pressure in the left coronary artery; i.e., the blood from the left coronary artery drains into the pulmonary artery,[4] and possibly because of the endocardial fibroelastosis usually associated with this anomaly.

Cause for Myocardial Ischemia: In cases of anomalous origin of the left coronary artery from the pulmonary trunk, the associated myocardial ischemia has been documented electrocardiographically many times since the report in 1933 of Bland, White and Garland.[14] Nevertheless, the cause of the ischemia has not met uniform recognition. The basis of disagreement revolved around the question, "In what direction does the blood flow in the artery arising anomalously from the pulmonary trunk?" Until recently the view most commonly held was that blood flows from the pulmonary trunk into the anomalous coronary artery and thence to the myocardium.[15] But lately, by means of angiocardiography, it has been proved that blood flows from the aorta to the normal right coronary artery, then to the anomalous left coronary artery via small anastomotic channels and finally drains into the pulmonary artery.[4]

This proves the observation that in some cases of cyanotic cardiac disease the level of oxygen saturation of arterial blood is far below that of venous blood of patients without right to left shunts. Cyanotic patients do not manifest clinical or pathologic signs of myocardial ischemia, however. Actually, it may not be the level of oxygen saturation but the low perfusion pressure supplied to the anomalous artery that makes the myocardium ischemic. In the presence of mitral regurgitation the perfusion pressure is even lower.

Diagnosis: The diagnosis of this syndrome is sometimes difficult to establish. However, in this disease cardiac enlargement is common and left ventricular failure frequent. Four proved cases of this entity have recently been added to the group having this rare anomaly.

The diagnosis was made angiocardiographically by a characteristic thinning of the myocardium near the apex and by the absence of pulsations of the huge left ventricle.[5] Most recently, by means of cineangiocardiography after direct injection of radiopaque substance in the coronary sinus by placing the tip of the catheter at the root of the aorta,[4,5] the entire course of blood flow in the anomalous coronary system has been established. In this particular case the congenital anomaly was found in the operating room during thoracotomy for a suspected patent ductus arteriosus with a classic machinery murmur at the base of the heart.

The electrocardiogram can be considered pathognomonic of aberrant origin of coronary artery from pulmonary artery only in the absence of mitral regurgitation.

In many patients an aneurysmal thinning of the apex of the heart is described which may be important if an electrocardiographic pattern of small R waves is obtained in V_1 to V_3.

The presence of mitral regurgitation is easy to establish clinically because of the loud pansystolic apical murmur. The variation of the murmur with position and respiration is unusual in rheumatic mitral regurgitation.

The recent advances in radiologic technic promise a great deal regarding early diagnosis.

The surgical treatment of this syndrome is still unsatisfactory and longevity is regulated chiefly by the degree of collateral circulation from the normal right coronary artery. Correction of the valvular defect can only be considered palliative as long as the vascular anomaly persists.

Summary

A case of aberrant origin of the left coronary from the pulmonary artery is described in a woman who lived to the age of twenty-six. In addition, severe mitral regurgitation was present due to a dilated and partially calcific mitral valve.

The clinical syndrome is reviewed and the causes for the myocardial ischemia outlined.

Angiocardiography is helpful in establishing the diagnosis. Electrocardiograms may be considered pathognomonic of the syndrome only in the absence of mitral regurgitation.

Surgical treatment still is unsatisfactory.

References

1. Abrikosoff, A. Aneurysma des linken Herzventrikels mit abnormer Abgangstelle der linken Karonaterie von der Pulmonalis dei eimen fienfomanthchin Kinde. *Virchows Arch. path. Anat.*, 203: 413, 1911.
2. Carrington, G. and Krumbhaar, E. B. So-called idiopathic cardiac hypertrophy in infancy. *Am. J. Dis. Child.*, 27: 449, 1924.
3. George, J. M. and Knowlan, D. M. Anomalous origin of the left coronary artery associated with rheumatic mitral insufficiency. *New England J. Med.*, 261: 993, 1959.
4. Lampe, C. F. J. and Verheugt, A. P. Anomalous left coronary artery. Adult type. *Am. Heart J.*, 59:769, 1960.
5. Lang, E. K., Phillips, L. A. and McAfee, J. G. Angiocardiographic features of the Bland-White-Garland syndrome. *Am. J. Roentgenol.*, 80: 381, 1958.
6. Swan, H. J. C., Zapata-Diaz, J., Burchell, H. B. and Wood, E. H. Pulmonary hypertension in congenital heart disease. *Am. J. Med.*, 16: 12, 1954.
7. Bland, E. F., White, P. D. and Garland, J. Congenital anomalies of the coronary arteries: report of an unusual case associated with cardiac hypertrophy. *Am. Heart J.*, 8: 787, 1933.
8. Kaunitz, P. Origin of left coronary artery from pulmonary artery: review of the literature and report of two cases. *Am. Heart J.*, 33: 182, 1947.
9. Bentivoglio, L. G., Uricchio, J. F., Woldow, A., Likoff, W. and Goldberg, H. An electrocardiographic analysis of sixty-five cases of mitral regurgitation. *Circulation*, 18: 572, 1958.
10. Swann, W. C. and Werthammer, S. Aberrant coronary arteries: experiences in diagnosis with report of three cases. *Ann. Int. Med.*, 42: 873, 1955.
11. Halpert, B. Arteriovenous communication between the right coronary artery and the coronary sinus. *Heart*, 15: 129, 1930.
12. Edwards, J. E. Anomalous coronary arteries with special reference to arteriovenous-like communications. *Circulation*, 17: 1001, 1958.
13. Eidlow, S. and Mackenzie, R. Anomalous origin of the left coronary artery from the pulmonary artery; report of a case diagnosed clinically and confirmed by necropsy. *Am. Heart J.*, 32: 243, 1946.
14. Black-Schaffer, B. Infantile endocardial fibroclastosis—a suggested etiology. *Arch. Path.*, 63: 281, 1957.
15. Case, R. B., Morrow, A. G., Stainsby, W. and Nestor, J. O. Anomalous origin of left coronary artery—the physiological defect and suggested surgical treatment. *Circulation*, 17: 1062, 1958.

Idiopathic Postural Hypotension

Case Report Including Hemodynamic Measurements before and after Acute Digitalization*

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WHEN A NORMAL subject assumes the upright posture, the arterial blood pressure is maintained by certain physiologic adjustments. Although initially there may be a 25 per cent fall in cardiac output and a decreased venous return, this is followed by an augmentation of cardiac output, compensatory arteriolar constriction and increased venous return. These adjustments assure maintenance of a normal cardiac output and prevent the fall of mean arterial pressure. Reflex mechanisms mediated via the sympathetic nervous system are thought responsible for these effects.[1]

In the patient with postural hypotension, however, three major aberrations of the normal response to assuming the upright posture have been observed: (1) a loss of reflex arteriolar constriction; (2) usually a fall but not necessarily a greater than normal fall in cardiac output which aggravates the blood pressure drop; and (3) inadequate venous return due to pooling of blood in the venous system. The present study was carried out in order to determine the effect of digitalization on these three parameters in a patient with idiopathic postural hypotension.

CASE REPORT

The patient was a seventy-four year old white man with a history of myocardial infarction in 1941. From 1942 to 1952 the patient was completely well, and did sedentary work full time. In 1952 there was an episode of sudden unconsciousness occurring spontaneously, which resulted in numerous bruises and lacerations but no neurologic sequelae. For the next six years the patient noted dizziness without tinnitus or hearing impairment and was seen by several physicians who treated him for Menière's disease despite the atypical nature of his symptoms. During his many consultations with physicians he received phenobarbital, belladonna, vitamins and reassurance, all without noticeable effect. The blood pressure was not measured in the erect position during this period of time.

In 1958, while driving his car, the occurrence of another episode of unconsciousness caused the patient's car to collide with another vehicle. Following this accident, during his three week hospitalization, postural hypotension was first documented. The patient could not remain standing motionless in the upright posture for more than a few minutes without lightheadedness, followed by collapse. Urinalysis, blood electrolytes, blood urea nitrogen and intravenous pyelogram were within normal limits. There was minimally impaired glucose tolerance without glycosuria. Urinary excretion of epinephrine and norepinephrine was not measured. None of the usual explanations of postural hypotension was present, such as varicosities, sympathectomy or ingestion of ganglionic blockers. A course of steroids proved therapeutically ineffective. He has obtained some relief of lightheadedness by wearing a rubber suit to the waist, and by regularly taking ephedrine.

Since his discharge from the hospital in 1958, the patient has had only two syncopal episodes, each lasting about three minutes. Syncope is avoided by sitting or lying down when dizziness occurs and therefore, he carries a small folding chair with him at all times. At present he is able to stand for only about thirty seconds without the rubber suit but he can walk long distances without dizziness or dyspnea and can sit comfortably for unlimited periods.

Physical examination revealed an intelligent, asthenic man who was able to stand for several minutes when wearing a rubber suit. Without the suit, cuff blood pressure was 150/95 mm. Hg recumbent, 130/80 sitting and 80/40 after thirty seconds in the erect posture, at which time the patient complained of

* From the Cardiopulmonary Laboratory, Grasslands Hospital, Valhalla, New York. This report is part of a study of the hemodynamic effects of cardiac glycosides now in progress and currently supported by the Westchester Heart Association.

TABLE I
Hemodynamic Measurements in Supine and Tilt Postures before and after Acute Digitalization

Measurement	Control			After Digitalis	
	Supine	Tilt	Recovery	Supine	Tilt
Right atrial pressure (mean) (mm. Hg)	+2	−2	+2	+2	−2
Radial artery pressure (mean) (mm. Hg)	115/72 (90)	73/46 (51)	113/55 (74)	191/88 (120)	118/67 (85)
Cardiac output (L./min.)	2.4	2.07	...	2.94	2.10
Cardiac index (L./min./M²)	1.48	1.28	...	1.81	1.29
Pulse rate (per min.)	75	78	75	72	72
Stroke volume (cc.)	32	27	...	41	29
Systemic vascular resistance (mm. Hg/L./min.)	37.5	24.5	...	40.8	44.8
Left ventricular work index (kg.M./min./M²)	2.4	1.3	...	4.9	2.2
Central blood volume (cc.)	600	604	...	637	592

dizziness. There was no dyspnea, orthopnea, distention of the neck veins, hepatomegaly or edema of the ankles. The lungs were clear and the heart was not enlarged. Atrial fibrillation was present with an apical rate of 90 per minute without pulse deficit. There were no murmurs. Both radial pulses were difficult to palpate. Brachial and other pulses were equal and intact bilaterally.

METHODS

A polyethylene catheter was passed via a thin walled No. 14 gauge needle in the left median basilic vein into the right ventricle monitored by the intracardiac electrocardiogram as previously described in this laboratory.[2] It was then withdrawn into the right atrium where it remained throughout the procedure. Measurements of arterial pressure were made via a No. 19 gauge indwelling needle in the right radial artery, using a Statham strain gauge and an electronic recording device.* Cardiac output was determined by the dye dilution method. The syringes containing the Cardio-Green® dye† were weighed before and after injection to determine the amount of dye injected.

After pressure measurements were made in the right ventricle and the catheter was withdrawn into the right atrium, the procedure progressed as follows: Intra-arterial and right atrial pressures were measured and immediately followed by recording of dye dilution curves. The patient was then tilted to 25 degree head-up position and pressures were repeated after two and one-half minutes of tilt, followed by dye outputs after three and one-half minutes. Recovery pressures were recorded after the patient had rested in the supine position for twelve minutes. Monitored by the electrocardiogram, acetyl strophanthidin was then injected intravenously at a rate of 0.12 mg. per minute until the total dose of 1.2 mg. had been given. This is the usual dose and method of administration in studies of this kind, and was assumed to be an adequate digitalizing dose.[3] Immediately thereafter, pressures and dye outputs were repeated with the patient supine. The patient was again tilted to 25 degree head-up position for two and one-half minutes. Pressures were recorded, followed by dye outputs at three and one-half minutes. There was no detectable strophanthidin toxicity during or for an hour after the procedure.

* Made by Electronics for Medicine, White Plains, New York.

† Obtained from Hynson, Westcott & Dunning, Inc., Baltimore, Md.

RESULTS

As seen in Table I, resting pressures were within normal limits but there was a reduction in cardiac output. Tilt resulted in a sharp decrease in radial arterial and right atrial pressures, a small decrease in cardiac output and a fall in systemic vascular resistance and left ventricular work index. Central blood volume was unchanged.

After digitalization, the usual pressor response to acetyl strophanthidin was noted.[4] Right atrial pressure and systemic vascular resistance remained at the recumbent pre-digitalis levels, but the cardiac output increased above the control level, and left ventricular work index doubled. Tilting after digitalis resulted in a drop in arterial pressure of similar magnitude

(35 mm. compared to 39 mm. Hg mean pressure drop) to that observed prior to digitalization, although the actual value was considerably above the pre-digitalis tilt level. The cardiac output fell to the same level as before digitalization. Systemic vascular resistance did not fall when the digitalized patient was tilted. Left ventricular work index decreased. There was little change in pulse rate throughout the procedure.

A few days after the procedure, the patient was digitalized orally. This medication has not resulted in any detectable clinical improvement.

Comments

The observed aberrations of the normal response to assuming the upright posture include a loss of reflex arteriolar constriction, a fall in cardiac output which aggravates the blood pressure drop and inadequate venous return; therefore, this case and the subject of postural hypotension may be discussed in the light of these differences.

Patterns of Responses in Postural Hypotension: Arteriolar vasoconstriction was obviously inadequate to maintain the blood pressure of this patient in the erect posture since the 25 degree head-up tilt resulted in hypotension and a lowered systemic vascular resistance. Hickam and Pryor[5] have described the normal postural response as no change in the mean arterial blood pressure, a 25 per cent decrease in cardiac output and a 33 per cent increase in systemic vascular resistance. In studying twelve cases of postural hypotension they have observed three particular patterns of variation from the normal response. In the first instance there was a large fall in arterial blood pressure despite the presence of a normal decrement in cardiac output, suggesting predominance of a defect in arteriolar vasoconstriction. Secondly, in some patients there was only a slight postural fall in blood pressure accompanied by a large fall in cardiac output on assuming the erect posture. In this situation there was some, but not a completely compensatory, rise in systemic vascular resistance, suggesting that there was less alteration in the normal reflex arteriolar constrictor mechanism. The third pattern of variation was illustrated by patients with concomitant large falls in blood pressure associated with large falls in cardiac output on tilting and little change in systemic vascular resistance. The third pattern being most common, the authors concluded that postural hypotension was primarily dependent on inadequate arteriolar tone and that it was often intensified by large drops in cardiac output on standing erect.

Inadequate Arteriolar Resistance: That the arterioles are still capable of responding with vasoconstriction has been shown in the study just described and by others. Acute digitalization of the patient with postural hypotension described in the present study prevented the drop in systemic vascular resistance with head-up tilt, but did not prevent either the fall in cardiac output or the decline in arterial pressure. Similarly, an infusion of norepinephrine can maintain blood pressure in such patients even in the erect position[6] and a preparation of norepinephrine in oil has been shown to maintain blood pressure for an hour.[7] The arterioles are thus capable of responding to exogenous norepinephrine, at least temporarily. The response to endogenous norepinephrine has not been clarified, however. Luft[7] has observed two subjects with postural hypotension who did not manifest the normal increase in urinary catecholamines after stimulation with intravenous insulin or histamine, who could excrete infused norepinephrine normally, but whose daily spontaneous catecholamine excretion was low. Such patients may have a defect in endogenous production of noradrenalin or utilization in response to physiologic stimuli.

Restricted Cardiac Output: In contrast to the emphasis given inadequate arteriolar constriction in the pathogenesis of postural hypotension, Weissler's work[8] stresses the inability of the heart to respond with an augmented cardiac output when confronted with a sudden decrease in peripheral resistance (tilt or assuming the upright posture). He attributes the restricted cardiac output to the limited venous inflow because inflation of the antigravity suit resulted in rapid reversal of the syncopal reaction without change in the peripheral resistance. Although these observations were made on normal students in whom abnormal postural responses were induced by premedication with sodium nitrite followed by tilting to 60 degrees, similar results have been reported in patients with postural hypotension following an albumin infusion. Hickam[5] rapidly infused 1,300 cc. of saline containing 75 gm. of human serum albumin into five subjects. In each case cardiac output and mean arterial pressure during tilt were improved after the infusion. As Warren[9] has stated, the cardiac output is "the servant rather than the

director of circulatory activities" in postural hypotension. If adequate venous return is provided through normal or artificial means, cardiac output can be maintained when peripheral resistance suddenly drops.[10]

Similarly, the cardiac output fell in the patient described in the present report, probably as a result of the decreased venous return during tilt. It is clear from clinical observations alone that even in the patient with frank congestive failure, poor myocardial function *per se* does not result in postural hypotension. Since the improvement in supine cardiac output following digitalization did not ameliorate the drop in cardiac output during tilt, the finding of a subnormal supine cardiac output in the present patient must be regarded as unrelated to the etiology of his postural hypotension.

Venous Return and Effect of Digitalis: Since increasing the blood volume by infusion and presumably thereby increasing venous return corrects the postural hypotension, at least temporarily, the behavior of the venous system under the influence of tilt and digitalis is pertinent. When the normal subject is tilted, there is a momentary imbalance between left ventricular output and systemic venous return. The intrathoracic blood depot, particularly the reserve of blood in the lungs, provides ample venous return to the left heart and postural hypotension is prevented.[11] Contrary to what one would expect in normal subjects, Page et al.[12] have shown that tilting results in an increase in central venous pressure and reflex generalized venoconstriction.

In the patient with postural hypotension, these mechanisms are faulty during tilt, resulting in inadequate compensation from the central venous reservoir (a decrease in both pulmonary and systemic venous return) with an ensuing fall in left heart output, cerebral insufficiency and fainting. The central venous pressure falls and peripheral venoconstriction is minimal. The present patient demonstrated the fall in right atrial pressure on tilting. Peripheral venomotor response was not measured. One may speculate that he could remain erect if he continued walking because an auxiliary mechanism, muscular activity, probably provided sufficient pulmonary venous return to prevent the fall in cardiac output.

It is of interest that measurements of central blood volume supine and during tilt before and after digitalization revealed no change. This may indicate that the cardiopulmonary reserve of blood was not mobilized in response to postural demands despite its availability or, for some unknown reason, left and right heart outputs were equally impaired. In either case, venous return to the left heart was inadequate. It is more likely that whatever small changes occurred could not be measured by the Stewart-Hamilton method since successive measurements of central blood volume even in normal subjects may vary by as much as 200 cc.[13]

Digitalization did not alter the right atrial pressure or the cardiac output response to tilt in our patient despite its seemingly beneficial effect in the supine position. This observation is in keeping with the findings of others[14,15] on normal hearts or enlarged hearts without failure in which there was no significant alteration of the venous pressure following digitalization. Harvey et al.[14] point out, however, that a peripheral action of digitalis may be too small to be detected or may be obscured by rapid venous adjustments, or may not influence central venous or right heart filling pressures. On the other hand, the experiments of Cotten and Stopp[16] with dogs demonstrate that ouabain does decrease venous return in a normal dog, and this reduction in the amount of blood filling the ventricles prevents the measured increased myocardial contractility from being translated into an increased cardiac output. When the venous return was prevented from decreasing by transfusion, cardiac output increased in the normal animal following digitalization. Thus, in this subject with postural hypotension, although digitalis probably had a positive inotropic effect in the supine position it is doubtful whether in the tilted position this increased myocardial contractility could have been converted to an augmented cardiac output because of the impaired venous inflow. In the supine state, when venous inflow was presumably adequate, an increase in cardiac output was seen after acute digitalization. In the present patient, at least, the peripheral effects of acetyl strophanthidin overshadowed the cardiac effects.

Rado et al.[17] have alluded to a mechanism providing for parallel changes in arterial and venous tone, and have demonstrated the coexistence of increased arterial and venous tone in arterial hypertension, heart failure and shock. Postural hypotension further illustrates their concept in a negative sense since it presents a situation in which there is a parallel deficiency in both arteriolar and venomotor tone.

Summary

In a seventy-four year old male patient with postural hypotension, measurements of arterial pressure, right atrial pressure and cardiac output were made in the supine position and during 25 degrees of head-up tilt before and after acute digitalization. On tilting there was a fall in arterial pressure, right atrial pressure, cardiac output, systemic vascular resistance and left ventricular work index. Following digitalization there was no change in right atrial pressure; there was a systemic arterial pressor response, an improvement in supine cardiac output, a slight increase in systemic vascular resistance and doubling of left ventricular work index. During tilting after digitalization measurements of cardiac output and stroke volume were unchanged from the measurements before digitalization, but the arterial blood pressure did not fall as low, and systemic vascular resistance and left ventricular work index were therefore higher than pre-digitalis values.

These findings are discussed in terms of the defects in reflex arteriolar and venous constriction and in myocardial function in idiopathic postural hypotension.

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References

1. Rushmer, R. F. Cardiac Diagnosis, p. 61. Philadelphia, 1955. W. B. Saunders Co.
2. Zohman, L. R. and Williams, M. H., Jr. Percutaneous right heart catheterization using polyethylene tubing. *Am. J. Cardiol.*, 4: 373, 1959.
3. Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., de J. Macias, J., Schreinder, B. F. and Lux, J. J. Studies of pulmonary hypertension. VIII. Effect of acetyl strophanthidin on pulmonary circulation in patients with cardiac failure and mitral stenosis. *Am. Heart J.*, 54: 235, 1957.
4. Williams, M. H., Jr., Zohman, L. R. and Rattner, A. C. Hemodynamic effects of cardiac glycosides in human subjects during rest and exercise. *J. Appl. Physiol.*, 13: 417, 1958.
5. Hickam, J. B. and Pryor, W. W. Cardiac output in postural hypotension. *J. Clin. Invest.*, 30: 401, 1951.
6. Scherba, E. J. Orthostatic hypotension and orthostatic tachycardia. *Am. J. Med.*, 17: 880, 1954.
7. Luft, R. and Von Euler, U. S. Two cases of postural hypotension showing a deficiency in release of nor-epinephrine and epinephrine. *J. Clin. Invest.*, 32: 1065, 1953.
8. Weissler, A. M., Warren, J. V., Estes, E. H., Jr., McIntosh, H. D. and Leonard, J. J. Vasodepressor syncope: Factors influencing cardiac output. *Circulation*, 15: 875, 1957.
9. Warren, J. V. Control of cardiac output in man. In: Work and the Heart, p. 57. Edited by Rosenbaum, F. F. and Belknap, E. L. New York, 1959. Paul B. Hoeber.
10. Guyton, A. C. The venous system and its role in the circulation. *Mod. Concepts Cardiovasc. Dis.*, 27: 483, 1958.
11. Brecher, G. A. Venous Return, p. 24. New York, 1956. Grune & Stratton.
12. Page, E. B., Hickam, J. B., Sieker, H. O., McIntosh, H. D. and Pryor, W. W. Reflex venomotor activity in normal persons and in patients with postural hypotension. *Circulation*, 11: 262, 1955.
13. Fritts, H. W., Jr. and Cournand, A. Physiological factors regulating pressure flow and distribution of blood in the pulmonary circulation. In: Pulmonary Circulation, p. 70. Edited by Adams, W. and Veith, I. New York, 1959. Grune & Stratton.
14. Harvey, R. M., Ferrer, I., Cathcart, R. T. and Alexander, J. K. Some effects of digoxin on the heart and circulation in man. *Circulation*, 4: 366, 1951.
15. Dimond, E. G., Lown, G., Luisada, A. A. and Chen, K. K. Panel discussion. In: Digitalis, p. 208. Compiled and edited by Dimond, E. G. Springfield, 1957. Charles C Thomas.
16. Cotten, M. De V. and Stopp, P. E. Action of digitalis on the nonfailing heart of the dog. *Am. J. Physiol.*, 192: 114, 1958.
17. Rado, J. P., Gonda, E. and Kovacs, E. The role of venous constriction in circulatory disorders. *Brit. Heart J.*, 20: 389, 1958.

Sinoatrial Heart Block with Wenckebach Phenomenon*

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THE ARRHYTHMIA to be discussed, sinoatrial heart block with Wenckebach phenomenon, is frequently unnoticed by the subject. Its detection and significance may escape the physician not alerted for its occurrence.

Sinoatrial heart block has been known to the medical profession since MacKenzie's description in 1902.[1] The Wenckebach phenomenon in sinoatrial heart block has appeared to be of greater rarity than the simple omission of complete heart beats. In 1906 Wenckebach[2] and later, in 1908, Rihl[3] described such a physiologic mechanism quite clearly. These were reiterated later by Wenckebach and Winterberg.[4] The occurrence of the Wenckebach type of block in this arrhythmia is not too surprising in view of the frequency with which it is noted in other types of cardiac conduction disorders. The paucity of reports would suggest that this arrhythmia is quite rare but this does not appear to represent the true incidence of this abnormal rhythm. We have seen four cases within a period of only a few months, three of them of clinical importance.

This arrhythmia may be associated with the intake of digitalis and probably represents a toxic cardiac effect of the drug. The clinical similarity to a sinus arrhythmia in spacing and rate underlines the need for careful clinical and electrocardiographic observation of the patient receiving digitalis. The following cases demonstrate the diversity of clinical manifestations of the disorder.

CASE REPORTS

CASE 1. An eighty-two year old man was first admitted to the hospital in 1957 because of pain on motion of the right hip. He had suffered an inferior myocardial infarction in 1955. He denied having any symptoms of heart failure or angina. General examination revealed a well oriented, elderly man. There was no venous distention and the examination of the chest revealed only fine rales at the right base. The blood pressure was 110/70 mm. Hg with a regular pulse of 68 beats per minute. The heart was not enlarged; there was a grade 2 basal systolic murmur. The painful right hip was found to be due to hypertrophic arthritis. An electrocardiogram revealed a sinus rhythm, evidence of old inferior myocardial infarction and an intraventricular conduction disturbance.

He was readmitted to the hospital in September 1959 because of increasing dyspnea. During the preceding two months he had experienced an anterior myocardial infarction; recovery was uneventful except for moderate congestive heart failure requiring maintenance doses of digitalis. He had stopped taking the digitalis in late August. Although he had been seen by his doctor and treated with a diuretic early on the day of admission, severe dyspnea developed upon arrival in the lobby of the hospital. He became cyanotic, had a convulsion and was in apparent cardiac arrest. Immediate blows to the chest followed by a 300 ml. phlebotomy and nasal administration of oxygen produced recovery from the acute episode. After being transferred to his room, intravenous digitalization was initiated. Physical examination at this time revealed an irregular tachycardia of 120 beats per minute with a blood pressure of 110/80 mm. Hg. Respirations were 32 per minute with bilateral moist rales up to the apices. The liver was tender and enlarged and scrotal and pretibial edema were noted. He received a total of 1.2 mg. of deslanoside within the next three hours.

The electrocardiogram revealed a variable rhythm with sinus beats interrupted by multiple supraventricular extrasystoles, periods of 2:1 sinoatrial block and periods of paroxysmal atrial tachycardia (160 beats per minute) with a 2:1 block. Further digitalis was withheld. The next morning the patient's congestive failure was worse and digoxin (1 mg. over the succeeding twenty-four hours) was administered. The electrocardiogram taken the next morning revealed occasional supraventricular extrasystoles with a sinus rhythm at a rate of 70 beats per

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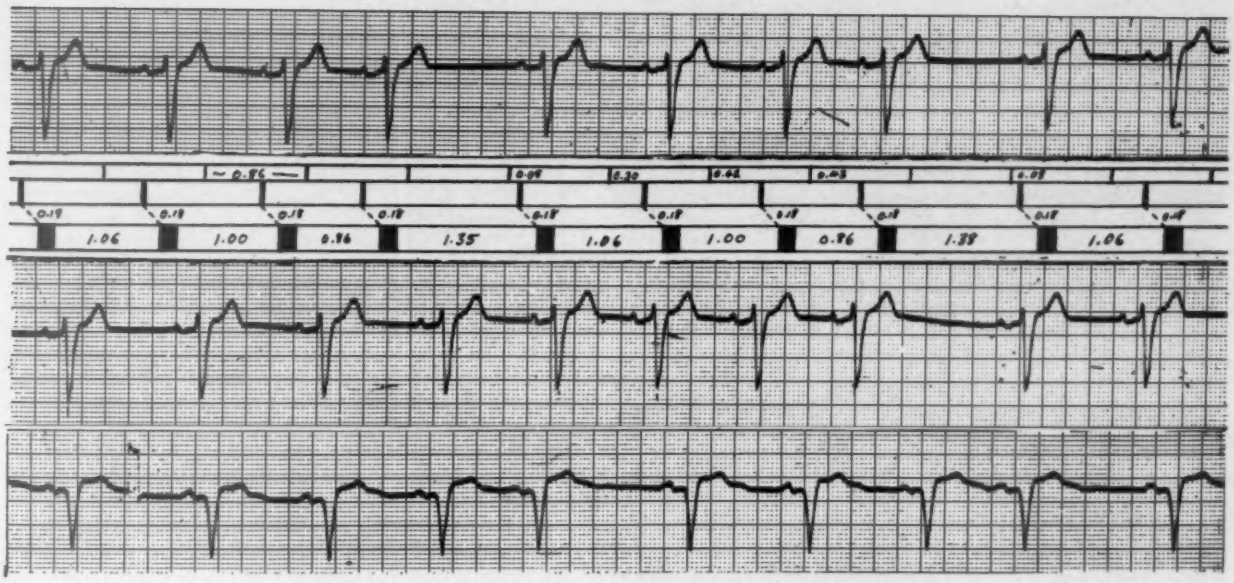

FIG. 1. Case 1. The upper strip of the continuous lead V_3R is diagrammed and shows two episodes of 5:4 sinoatrial heart block with the Wenckebach phenomenon. The diagram assumes an 0.08 second initial conduction between sinoatrial node and atrial muscle. The middle strip shows a single 9:8 response which requires a nearly ten second recording for its demonstration. Note that while the P-P and R-R intervals become shorter until a dropped beat occurs the P-R interval does not change. In the lower strip lead III shows the same mechanism with 6:5 and 5:4 response.

minute. The condition of congestive failure seemed improved and a review of the electrocardiograms strongly suggested digitalis toxicity; therefore, no further digoxin was given for three days. However, it gradually became obvious that diuretics were not sufficient to control the failure and administration of digoxin was resumed at a dose of 0.25 mg. daily. Three days later the tracing shown in Figure 1 was obtained. The following day a ventricular bigeminal rhythm was observed and administration of digoxin was stopped. As before, congestive failure developed slowly despite diuretics and after a lapse of five days digoxin was again administered at a dose of 0.25 mg. daily. Two days later a marked sinus bradycardia of 44 beats per minute was observed but long strips did not reveal confirmatory evidence for sinoatrial heart block. The bradycardia reverted spontaneously the next day to a sinus rate of 70 beats per minute with only occasional ventricular extrasystoles at a fixed coupling.

Summary: This elderly man, who had had two myocardial infarctions, was admitted with severe congestive failure. Immediate treatment reversed an acute episode on admission but the patient exhibited marked sensitivity to digitalis. On one occasion this was heralded by the variable sinoatrial heart block illustrated in Figure 1 and on a second occasion by a slow rate of heart beat which may have been due to 2:1 sinoatrial block. On each occasion subsequent electrocardiograms revealed fixed ventricular coupled extrasystoles and more classic evidence of digitalis toxicity.

CASE 2. A seventy-five year old woman had multiple hospital admissions since 1933. Initially she had no clinical evidence of cardiovascular disease. The first electrocardiogram, taken in 1950, revealed a sinus tachycardia of 100 beats per minute with multiple extrasystoles. In 1952 the patient was given digitalis because of mild heart failure, and subsequent electrocardiograms in 1954 revealed a rate of 85 beats per minute with occasional atrial extrasystoles. In 1957 she began to experience occasional substernal pain which was relieved by nitroglycerin, and noted occasional episodes of dizziness. She exhibited signs of moderate right heart failure. The electrocardiogram revealed a basic rate of 75 beats per minute with multiple episodes of 2:1 sinoatrial heart block. Subsequent tracings revealed a bigeminal rhythm, similar to parts of Figure 2, suggesting 3:2 sinoatrial heart block. ACTH, given intravenously for bursitis in the shoulder, did not affect the electrocardiogram.

In 1959 she was admitted for syncope, the attack having occurred while she was shopping. Examination did not reveal any definite cause for the syncope and an electroencephalogram was within normal limits. The earlier findings of slight cardiac enlargement and slight right heart failure were again noted. Digitalis dosage was continued. The electrocardiogram revealed a variable sinoatrial heart block with Wenckebach phenomenon from 4:3 to 2:1 with a basic rate of 78 beats per minute.

She was readmitted in January 1960. She had

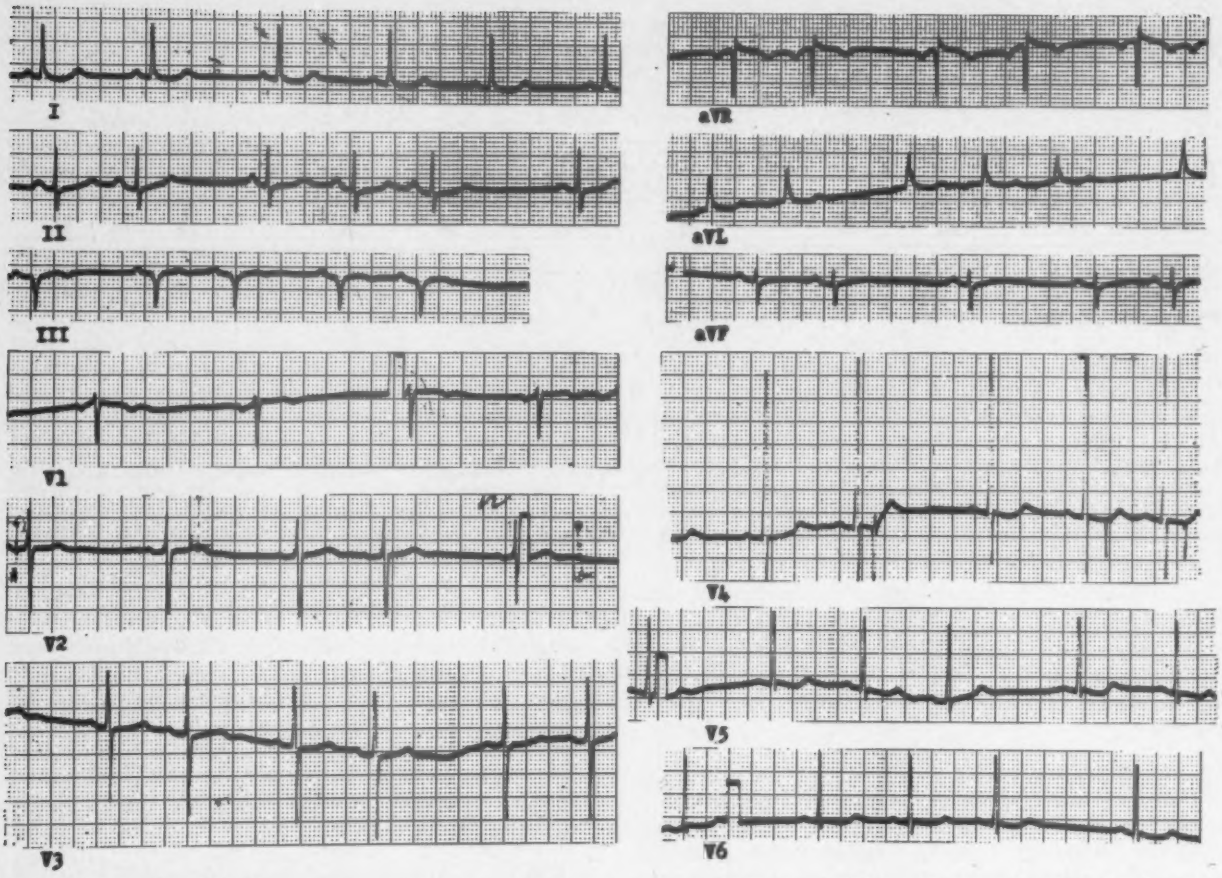

FIG. 2. Case 2. The first two complexes in lead II demonstrate a 3:2 sinoatrial heart block with the Wenckebach phenomenon, and the next three complexes a 4:3 response. Other leads are similar except for lead V_1 where a 2:1 sinoatrial heart block without Wenckebach phenomenon is suggested in the first three complexes.

noted mild dyspnea on exertion since her admission the year before and had experienced several syncopal episodes of brief duration. She was still taking digitalis. The examination revealed a febrile woman with bilateral rales in the chest and dullness at the left base and right midlung field, attributed to bronchopneumonia. The blood pressure was 160/80 mm. Hg. There was no other evidence of congestive heart failure. The rate of heart beat was irregular. The electrocardiogram taken at this time is illustrated in Figure 2. The bronchopneumonia responded to antibiotic therapy and she was discharged.

Summary: An elderly woman, initially given digitalis for congestive heart failure, to which she at first responded well, subsequently had syncope and the electrocardiographic picture of sinoatrial heart block. It is of interest that ACTH, given for bursitis of the shoulder, did not affect the heart block.

CASE 3. An eighty-four year old man was admitted in January 1959 for cataract surgery. He had a history of coronary artery disease accompanied by angina pectoris, fainting from cerebral anoxia and paroxysmal atrial tachycardia. Examination revealed an elderly man in no distress with a blood pressure of 150/80 mm. Hg and a pulse of 45 beats per minute. There was moderate cardiac enlargement, confirmed by x-ray film of the chest. There were bilateral crepitant rales at the lung bases and good expansion of the chest. The electrocardiogram revealed a rate of 43 beats per minute with what were interpreted as atrial extrasystoles. The short R-R intervals corresponded to a rate of 70 beats per minute and there was no alteration of the P wave contour between the various beats on observation of the short lead strips available. This is more suggestive of intermittent 2:1 sinoatrial heart block. In view of the mild failure and electrocardiographic impression of atrial irritability, the patient was digitalized preoperatively. A regular rate of 52 beats per minute developed and he withstood surgery without difficulty. Postoperatively he experienced two attacks of precordial pain with syncope. No definite diagnosis was made for these, though heart block was suggested by one observer.

He was readmitted in January 1960 for further cataract surgery. Examination revealed dilated cervical veins, bilateral basal rales in the chest, slight cardiac enlargement and a palpably enlarged liver. The blood pressure was 220/100 mm. Hg and the

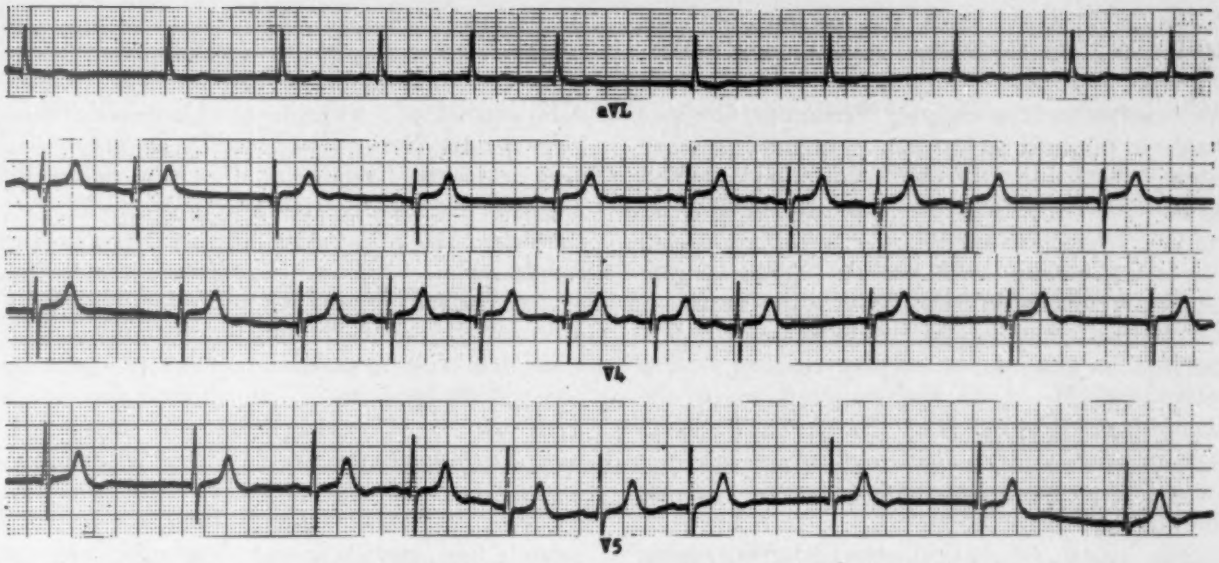

FIG. 3. Case 3. The upper strip, lead aVL, shows a 6:5 sinoatrial heart block with the Wenckebach phenomenon. The two middle strips are a continuous tracing of lead V_4 and show one 5:4 and one 7:6 episode, the latter followed by nodal rhythm. The lowest strip (V_5) shows a 6:5 response preceded and followed by nodal rhythm.

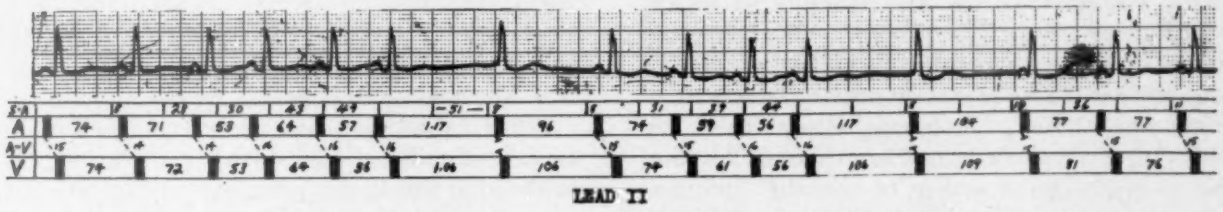

FIG. 4. Case 4. Lead II. This strip shows a more complex rhythm. Beginning with the second beat there is a series of five conducted beats, with slightly varying P-R interval, followed by a nodal escape beat. The diagram assumes an initial 0.08 second conduction time from sinoatrial node to atrial muscle. Assuming a regular sinoatrial nodal discharge every 0.51 second, there is a gradual delay in the sequence. The third beat shows a lesser increment of delay as the diagram is constructed, but may be the result of sinus arrhythmia. Two sinoatrial nodal impulses are blocked allowing time for a nodal escape. Starting with the eighth beat there is a series of four conducted beats showing a regular increment in sinoatrial-atrial conduction delay, clearly demonstrating sinoatrial heart block with the Wenckebach phenomenon. The next beat demonstrates a nodal escape.

pulse was 50 beats per minute and irregular. That evening the patient had a sudden attack characterized by pain in the left side of the chest, pallor, coldness, profuse sweating and, initially, an unobtainable pulse. An electrocardiogram revealed evidence of sinoatrial heart block with the Wenckebach phenomenon (Fig. 3). Serial electrocardiograms did not reveal any change except that the evidence of sinoatrial heart block disappeared as the congestive failure was corrected with diuretics. The patient maintained a regular pulse of 60 beats per minute and digitalis was withheld. He was discharged without surgery.

Summary: This elderly man with severe arteriosclerotic heart disease had multiple syncopal episodes when digitalis was given, but felt well on a program of diuretics alone. Several electrocardiograms have shown sinoatrial heart block with Wenckebach phenomenon.

CASE 4. A sixty year old woman was admitted in July 1959 for "chronic brain syndrome," complaining of pain in the right hip due to a fracture. She was psychotic and disoriented; therefore, history was obtained from a relative who stated that the patient was a diabetic, was hypertensive and had been blind since an unsuccessful operation for the removal of cataract had been performed fourteen months previously. The family had noted progressive mental deterioration.

Examination revealed a regular heart rate of 80 per minute and a blood pressure of 178/120 mm. Hg. X-ray of the chest revealed an increase in the bronchovascular markings and cardiomegaly with left ventricular predominence. The electrocardiogram taken four days after admission (Fig. 4) showed a complex rhythm with evidence of sinoatrial block and Wenckebach phenomenon.

Urinary and wound infection occurred and terminally a staphytococcic, generalized furunculosis developed. An autopsy was not granted.

Summary: This elderly woman with diabetes had a routine electrocardiogram taken which showed evidence of sinoatrial block and Wenckebach phenomenon. Serious cardiac disease was not evident until overwhelming urinary and wound infection had developed, which proved fatal.

Comments

Electrocardiographic Diagnosis: In order to demonstrate clearly this arrhythmia it is important to observe the cardiac rhythm over a period of fifteen to twenty seconds in the electrocardiographic lead where the P waves are seen best. Several of our cases would not have been diagnosed had only the routine mountings been observed.

The most important electrocardiographic distinction to be made is between sinoatrial heart block with the Wenckebach phenomenon and sinus arrhythmia. There is no change in the atrial complex, in the P-R interval or in the ventricular complex in either rhythm. Slowing of the rate of heart beat with expiration and its quickening with inspiration are characteristic of sinus arrhythmia. Electrocardiographically, this may be seen as a gradual lengthening followed by a gradual shortening of the P-P interval, and, consequently, the R-R interval; thus, a bellows or accordian type of record is obtained. Sinoatrial heart block may be associated with sinus arrhythmia but in its usual form it is characterized by a regular rhythm with the abrupt omission of a complete complex which results in a space or pause. The kind discussed here, sinoatrial heart block with Wenckebach phenomenon, shows a variable spacing clearly described by Wenckebach and Winterberg[4] and later by Sir Thomas Lewis.[5]

The distinction from sinus arrhythmia is indicated by the progressive decrease in the P-P interval with no succeeding gradual increase, but, instead, an abrupt omission of the entire heart beat. The failure to show a progressive increase, as in sinus arrhythmia, and the presence of a pause has led to the development of criteria for the electrocardiographic diagnosis of sinoatrial heart block with Wenckebach phenomenon. Winton[6] has stated three criteria: (1) the P-P interval including a blocked sinoatrial impulse is shorter than the double distance of the P-P interval preceding it; (2) the P-P interval after the dropped sinoatrial impulse is longer than the interval preceding the pause; (3) there is a gradual shortening of the P-P interval preceding the pause. It is important to re-emphasize that there is no change in the P-R interval. Figure 4 represents an exception to this general rule. As we have shown (Fig. 1), there may be a long series of beats with the rate becoming progressively shorter prior to the dropped beat; therefore, the importance of a long recording is apparent.

Experimental Work: Eyster,[7] by means of mechanical trauma to the area of the sinoatrial node, was able to produce periods of sinoatrial heart block in animals. He showed recordings from the area of the sinoatrial node demonstrating the formation of electrical impulses which were conducted to the atrial muscle with a progressively increasing interval of time even though the simultaneously recorded electrocardiogram revealed no evidence of this change. These tracings were recorded from the exposed heart by means of pairs of electrodes placed very closely together on the sinoatrial node and atrial muscle. Other peripheral recordings showed the typically progressive decrease in the P-P interval and abrupt pause.

Eyster's work was later criticized by Resnik[8] because of the technic employed. He did not believe that mechanical damage in and around the sinoatrial node was comparable to a clinical situation, and he utilized pituitary extract injections presumably to increase the vagal stimulation as his experimental procedure. No electrical records were obtained from the area of the sinoatrial node in this experiment and the possibility of Wenckebach phenomenon was not mentioned.

More recently, Scherf[9] injected various solutions into the sinoatrial node and was able by this means to precipitate sinoatrial heart block. Severing both vagus nerves in the neck did not prevent the appearance of the block. He believed that there is reflex inhibition of the sinus node centers due to the mechanical stimulus and did not consider that the nature of the injected substances was important in producing the block.

Kisch[10] has recently demonstrated in dogfish, in an exhausted, dying heart, the appearance of combined sinoatrial and atrioventricular heart block. He recorded the electrical discharges of the sinoatrial node area and observed a progressive lengthening of the sinoatrial-atrial muscle interval. In a slightly febrile rabbit he discovered that morphine, pressure on the larynx and reflexes from the

respiratory tract produced sinoatrial heart block.[11] Kisch believes that, as in this unusual rabbit, both increase in vagus tone and some underlying nodal pathology are involved in producing the manifestation of sinoatrial heart block.

There is no experimental evidence deciding the question of whether clinically observed sinoatrial heart block is the result of structural or functional changes. It is worth noting that the best demonstrations of sinoatrial block are obtained when the atrioventricular nodal pacemaker is sufficiently depressed so that it does not assume control of the heart.

Clinical Reports: No attempt has been made to summarize the entire literature on sinoatrial heart block since the communication by Barlow[12] in 1927 which brought the total number of reported cases to fifty-four. In a descriptive report Blumberger[13] demonstrated an unequivocal case of sinoatrial heart block with Wenckebach phenomenon in a fifty year old man receiving no drugs. He clearly described the mechanism of this type of sinoatrial heart block.

DeZarday[14] reported two cases of sinus block, and in one case he noted a gradual increase in the P-P interval up to the time when the dropped beat occurred. He believed that this gradual increase was a condition necessary to the Wenckebach phenomenon. The nature of this concept is easily understood when it is recognized that there is no electrocardiographic deflection at the time of sinoatrial nodal discharge. The electrocardiogram demonstrates the discharge occurring in the atrial and ventricular muscle and records the repolarization in these muscles. However, there is no electrocardiographic indication of impulse formation in the sinoatrial or atrioventricular nodes or in the Purkinje fibers. With the common concept that the P-R interval is accounted for wholly by the atrioventricular node delay, demonstration of nodal phenomenon in the electrocardiogram may be initially suggested. Careful consideration will, however, reveal that in the individual case, with each peculiar pathology, there is no available technic to confirm what electrical events transpire during isoelectric periods. This is true of the sinoatrial node, in which electrical activity is not observable clinically and has seldom been recorded experimentally.

Elucidation of the nature of the Wenckebach phenomenon in sinoatrial heart block requires the postulation of sinoatrial nodal impulses from the spacing of the P waves in the electrocardiogram. Experimental recording has revealed a progressive increase in conduction time from sinoatrial node to atrial muscle, or even complete sinoatrial node and atrial muscle dissociation, without change in the P wave in the peripheral electrocardiogram. The nature of the Wenckebach phenomenon in sinoatrial heart block requires the increment of increase in conduction time of each successively delayed impulse to be less than the increase in the preceding conduction time. This results in the arrival time of the P waves coming closer together and a quickening of the heart rate. As this is the mechanism of the block, DeZarday's description[14] that the P-P interval progressively increases up to the point of the dropped beat in sinoatrial heart block with Wenckebach phenomenon cannot be accepted. Re-examination of his electrocardiograms with the assumption of a more rapid rate of sinoatrial node discharge permits the above criteria for the Wenckebach phenomenon to apply and explains his electrocardiograms by postulating more than one dropped beat.

The alternative explanation for the clinically observed pauses is the complete failure of generation of the sinus node impulse. It should be made clear that the coexistence of sinus arrhythmia may make delineation of the peculiar spacing of sinoatrial heart block with Wenckebach phenomenon difficult. Although the experimental work cited, when it has included direct recordings from the sinoatrial node area, has demonstrated sinoatrial nodal impulses which were not conducted, the clinical possibility of failure of impulse formation cannot be excluded with certainty in the absence of such direct recordings. It seems doubtful, however, that the absence of a single impulse could account for the preceding mathematical acceleration of the cardiac rhythm consistently observed in this variation of sinoatrial heart block although in the absence of Wenckebach phenomenon it is as reasonable an explanation as any other. For these reasons, then, we do not believe that this mechanism applies to our patients.

Relationship to Drugs: In many cases of sinoatrial heart block digitalis has been administered. Three of our patients also had received this drug. In some of these cases there was evidence later of more characteristic arrhythmias suggesting that the appearance of

sinoatrial heart block with Wenckebach phenomenon had been an early indication of digitalis toxicity.

The importance of digitalis in producing sinoatrial heart block was pointed out many years ago by Bishop.[15] That it need not do so was recently stated by Winton[6] who noted that only four of his eleven patients had received digitalis. He noted, however, that all eleven patients had heart disease. All of our four patients had heart disease.

Atropine has been observed to abolish the arrhythmia in some cases, particularly in younger patients. The sympathomimetic amines have not had much effect in altering this arrhythmia.

The current availability of highly potent drugs, many with diffuse and still not fully appreciated side reactions, may lead to the more frequent observation of more unusual electrocardiographic syndromes. Two of our patients had received the newer thiazide diuretics. These drugs appear to have an effect on electrolytes and metabolism apart from their action on the renal tubules. Such drugs may potentiate the actions of older drugs, like digitalis, in unexpected ways, leading to unusual toxic manifestations.

Summary

Four cases of sinoatrial heart block with the Wenckebach phenomenon have been presented. All the patients were observed within a period of a few months and all but one had received digitalis in relation to the heart block. The importance of observation of long electrocardiographic tracings in the diagnosis of this disorder is emphasized. The possibility of sinoatrial heart block with Wenckebach phenomenon being an early manifestation of digitalis toxicity is suggested.

References

1. MacKenzie, J. The cause of heart irregularity in influenza. *Brit. M. J.*, 2: 1411, 1902.
2. Wenckebach, K. F. Beitrage zur Kenntnis der menschlichen Hertztatigkeit. *Arch. Anat. u. Physiol.*, 297, 1906.
3. Rihl, J. Klinischer Beitrag zurkenntnis der Ueberleitungsstorungen von der Bildungsstate der Ursprungsreize zum Vorhof. *Deutsches Arch. klin. Med.*, 94: 286, 1908.
4. Wenckebach, K. F. and Winterberg, H. Die Unregelmassige Herztatigkeit und Ihre Klinishe Bedeutung, p. 75. Leipzig, 1914. W. Englemann.
5. Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, 3rd ed., p. 411. London, 1925. Shaw and Sons, Ltd.
6. Winton, S. S. Sino-auricular block. An analysis of eleven cases. *Acta cardiol.*, 3: 108, 1948.
7. Eyster, J. A. E. and Meek, W. J. Experiments on the origin and conduction of the cardiac impulse. VII. Sinoventricular and sinoauricular heart block. *Arch. Int. Med.*, 19: 117, 1917.
8. Resnik, W. A. The nature of so-called sino-auricular block. *Arch. Int. Med.*, 36: 788, 1925.
9. Scherf, D. Experimental sino-auricular block. *Proc. Soc. Exper. Biol. & Med.*, 61: 286, 1946.
10. Kisch, B. Wenckebach periods in sinoauricular block. *Exper. Med. & Surg.*, 6: 447, 1948.
11. Yuceoglu, Y. Z. and Kisch, B. Periodic sinoauricular block in animal experiment. *Exper. Med. & Surg.*, 13: 197, 1955.
12. Barlow, P. The clinical occurrence of sinoauricular block. *Lancet*, 212: 65, 1927.
13. Blumberger, K. Die Unterscheidung zwier Typen von sinaurikularen Block. *Deutsche med. Wchnschr.*, 62: 1377, 1936.
14. DeZarday, I. Unusual features of two cases of sinus block. *Am. Heart J.*, 12: 339, 1936.
15. Bishop, L. F. and Bishop, L. F., Jr. Sinoauricular block due to digitalis. *New York J. Med.*, 29: 1195, 1929.

Unusual Cardiac Arrhythmias in Myocardial Infarction

A Case with S-A Block, Paroxysmal A-V Nodal Tachycardia with Varying 2:1 and 3:1 Block, Dissociation between Pacemakers Situated within the Conducting System and Premature Beats in A-V Rhythm and A-V Dissociation*

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SINOATRIAL BLOCK WITH coronary sinus rhythm is stated to be rare if indeed it exists at all.[1] Clinical reports of dissociation between two ectopic pacemakers, both situated within the A-V conducting system,[2–5] and of effects of premature beats upon A-V rhythm[6–9] are few. A case of myocardial infarction with a combination of these rare arrhythmias with several interesting features has, therefore, been considered worth recording.

CASE REPORT

A sixty year old man was first admitted to the hospital on February 2, 1959, when the first electrocardiogram was taken. He had a history of attacks of pain over the precordium and left shoulder during the last three months. He left the hospital two days later against advice and was readmitted on March 2, 1959. He had not taken any digitalis preparation.

On examination the pulse was slightly irregular with a rate of about 75 beats per minute, the blood pressure 160/100 mm. Hg, the heart was considerably enlarged and there was moderate congestive cardiac failure. A series of electrocardiograms were taken during his stay in the hospital. They showed paroxysmal A-V nodal tachycardia with varying A-V block until March 5, escape-capture type of bigeminal rhythm from March 5 to 14, and mostly A-V dissociation with ventricular capture beats from March 14 until the patient was discharged on April 18. Transient A-V rhythm was seen spontaneously on April 8 and during administration of Bellafolline from April 14 to 16.

ELECTROCARDIOGRAMS

Figure 1. *A*, taken on February 2, shows a pattern of inferior and anteroseptal myocardial infarction; elevated P-Q segments in leads II, III and aVF are suggestive of atrial infarction. The atrial rate is 172 per minute and ventricular rate, 86 per minute. The P waves are low positive in lead I, inverted in II, III and aVF and upright in aVR, indicating a focus low in the atrium near the atrial part of the A-V node or in the A-V node. Change in relation of the P waves to QRS suggests that the paroxysmal tachycardia is associated with 2 : 1 A-V block and variable conduction time or that there is A-V dissociation. Slowing of the ventricular rate with increase of block to 3 : 1 or 4 : 1 after carotid sinus pressure (bottom strip) shows the presence of the former.

B (upper three strips are continuous, bottom strip after carotid sinus pressure), taken on March 2, shows persistence of the ectopic tachycardia. The atrial rate is 162 per minute. The P-P intervals are absolutely constant at 0.37 second; the R-R intervals vary. Groups of faster beats are separated by longer ventricular pauses. The third, ninth, twelfth, thirteenth and sixteenth QRS complexes which terminate the longer pauses are conducted at a P-R interval of 0.34 to 0.36 second. The P-R intervals of the second to the sixteenth QRS complexes are 46, 34, 40, 44, 44, 45, 46, 36, 40, 46, 36, 36, 40, 46 and 34 (hundredths of a second), respectively, and the R-R intervals are 75, 99, 81, 78, 76, 76, 75, 101, 81, 79, 102, 112, 84, 75 and 100 (hundredths of a second), respectively. Thus, within the faster groups of beats the P-R interval progressively increases and the R-R

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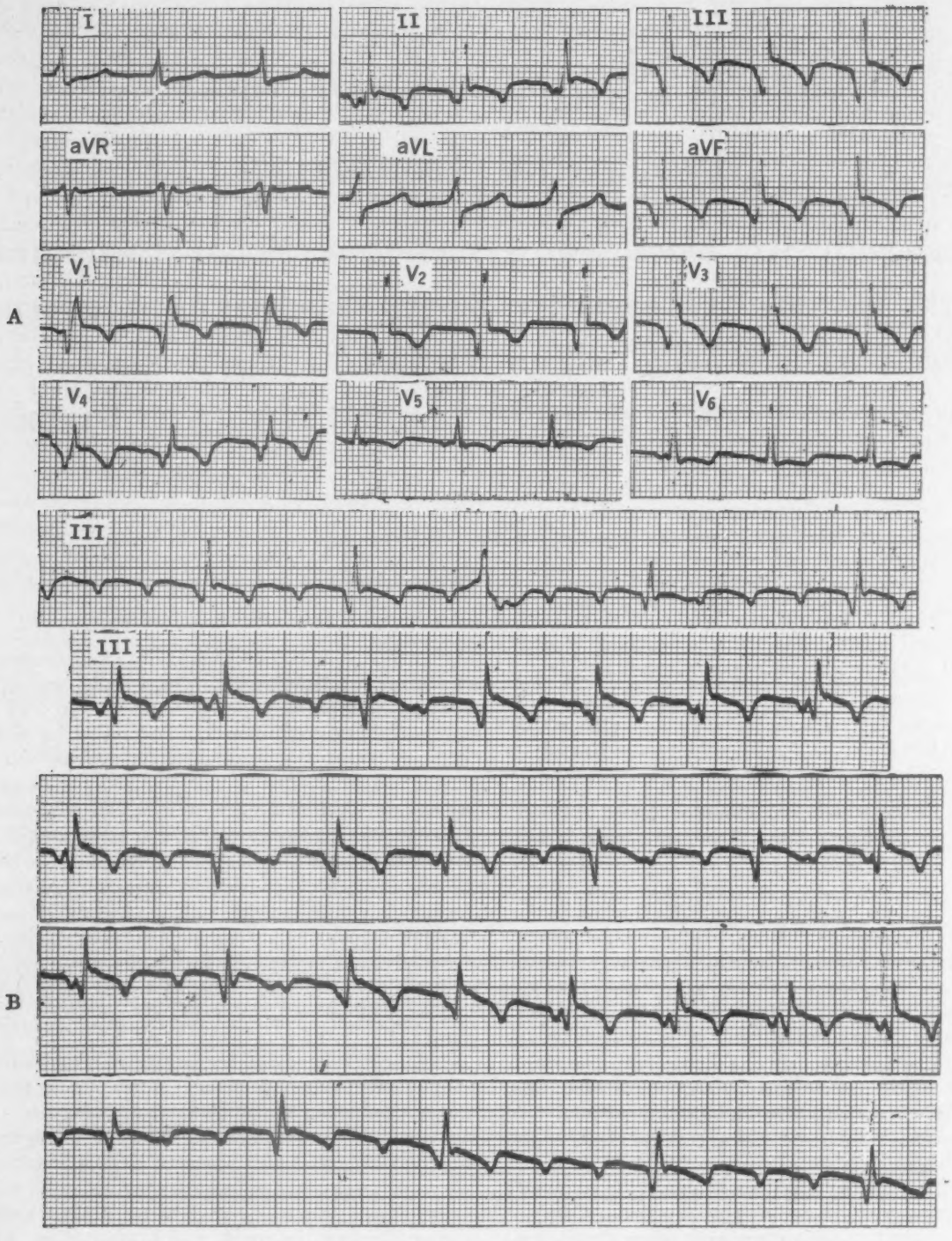

Fig. 1. A, taken on February 2, 1959; B, taken on March 2, 1959. See text.

interval decreases. The increasing P-R interval is clearly noted in the increasingly visible blocked P waves just preceding the QRS complexes. The last R-R interval before the pause is shorter than the first one after the pause except when there is 3 : 1 conduction in the twelfth and thirteenth successive beats when the R-R interval is three times the P-P interval. All this is characteristic of Wenckebach periods of the alternate effective impulses in the lower A-V junction, leading to 3 : 1 conduction in the beats terminating the long pauses. The bottom strip after carotid sinus pressure shows increase in block to 4 : 1.

Figure 2. A, electrocardiograms taken on March 5 show A-V dissociation with escape-capture bigeminy or reciprocal rhythm with first degree A-V block. The direction of the P waves is the same (other leads not shown here) as in Figure 1A demonstrating

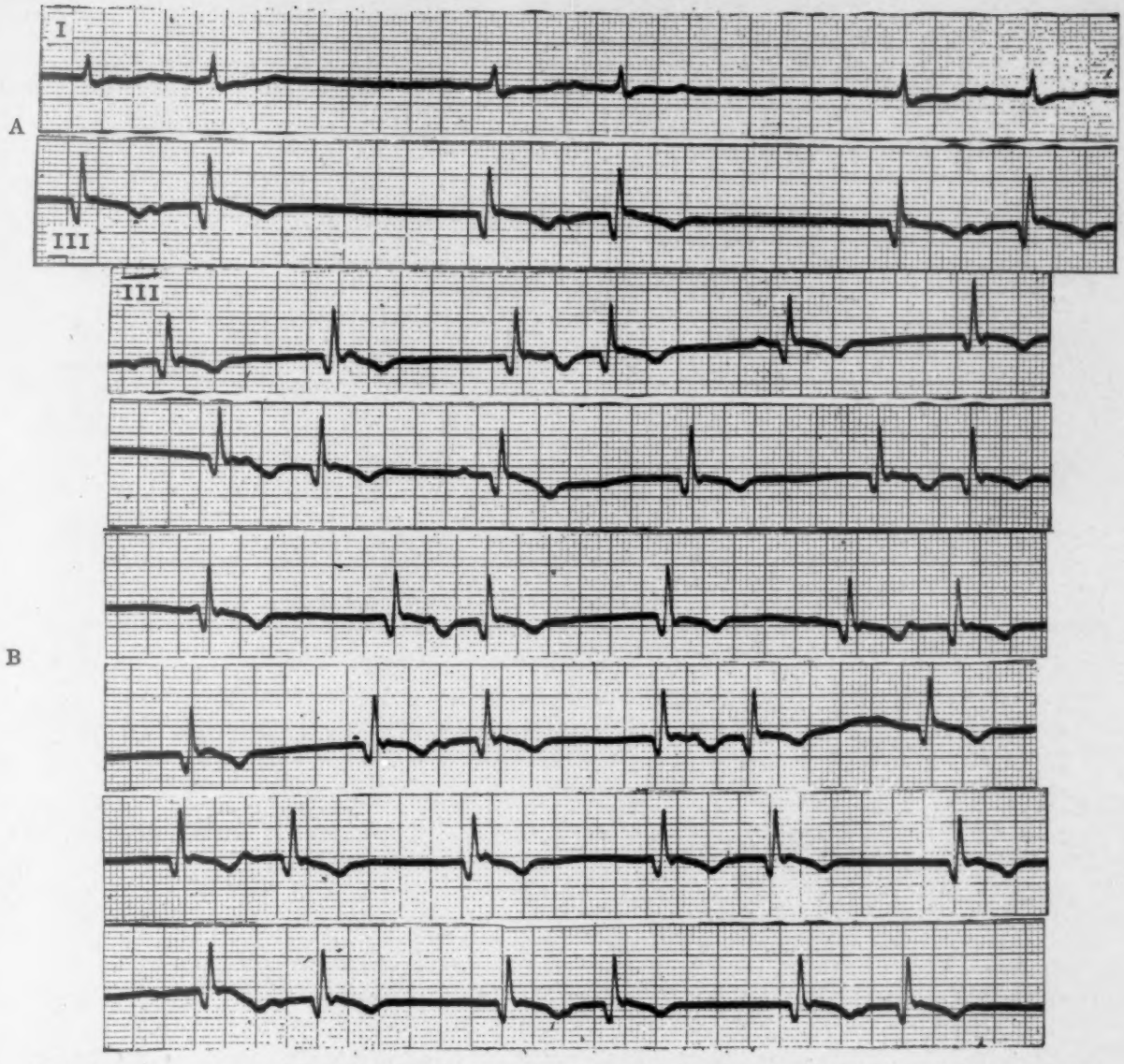

FIG. 2. A, electrocardiograms taken on March 5, 1959; B, taken after an intravenous injection of atropine. See text.

that the upper pacemaker is located low in the atrium or in the A-V node. Its rate is 22 per minute. The identical QRS contour of the escape and the conducted beat shows that the lower pacemaker is situated in the conducting system above the bifurcation of the bundle of His, probably in the lower part of the A-V node.

B (the strips are continuous), taken after an intravenous injection of 0.6 mg. atropine, suggests that the bigeminy in record A is due to A-V dissociation with capture beats and not to reciprocal rhythm. A change in relation of the P waves to the QRS is clearly seen in the fifth cycle in the first strip and third cycle in the second strip; there is considerable variation in the R-P (0.20 to 0.46 second) intervals and in the P-R (0.26 to 0.48 second) intervals of the conducted beats. The change in shape and direction of the P waves suggests a wandering pacemaker with intermittent shift of the atrial focus, probably to the sinus node. The last strip reveals return of the bigeminal rhythm with inverted P waves which continue with return to the original P-P intervals.

Figure 3. Electrocardiograms taken on March 14 when change of rhythm was again noted. There is A-V dissociation with ventricular captures. *A*, demonstrates inverted P waves in leads II, III and aVF. *B* (the three strips are cuttings from a long tracing of lead III), shows that the rate of the lower pacemaker is 33 per minute and that of the upper pacemaker varies between 22 and 33 with uneven P-P intervals varying between 1.80 and 2.60 seconds. The R-R intervals between the conducted beat and the next nodal escape are shorter than the internodal interval due to delay of the conducted impulse below the site of the escaping pacemaker. The P-P intervals

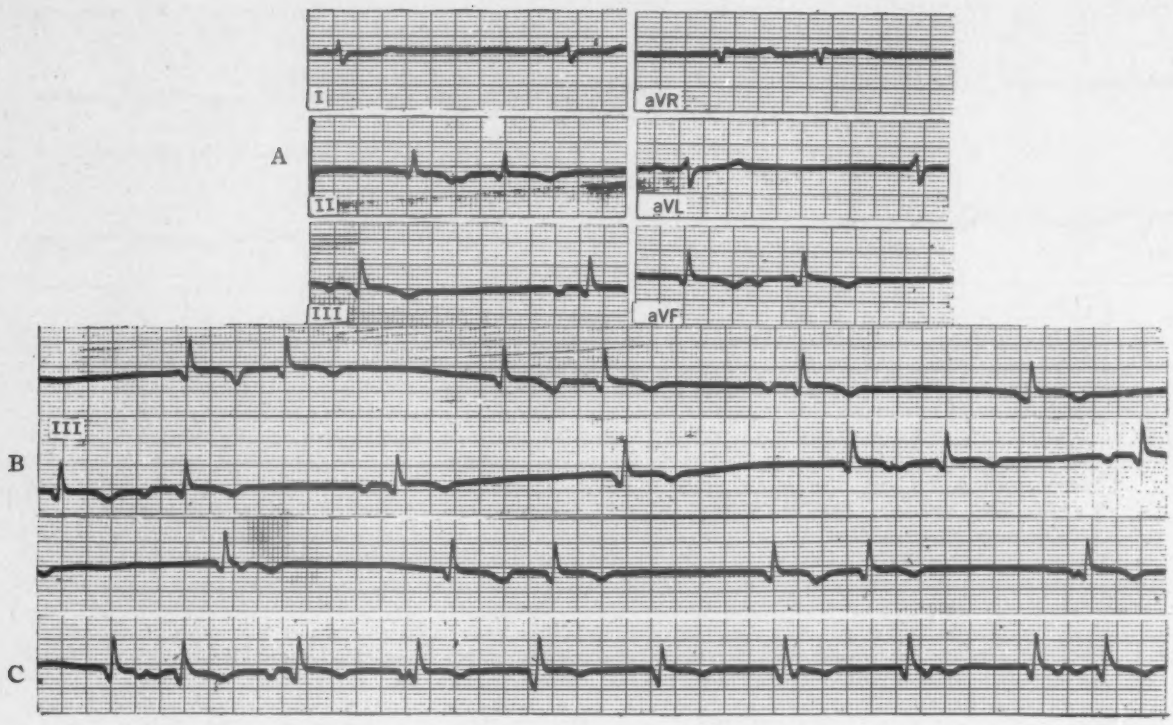

FIG. 3. Electrocardiograms taken on March 14, 1959. A, demonstrates inverted P waves in leads II, III and aVF; B, demonstrates rates of pacemakers; C, demonstrates abolition of the ventriculophasic arrhythmia and acceleration of rates of pacemakers after administration of atropine. See text.

which include the conducted QRS are usually shorter due to ventriculophasic arrhythmia. At two places the P-P interval lengthens to 2.6 seconds and gives rise to bigeminy. The P-P interval in the bigeminal rhythm in Figure 2A is similar (2.64 seconds). *C*, taken after intravenous injection of 1.2 mg. atropine, shows abolition of the ventriculophasic arrhythmia and acceleration of the rates of the upper and the lower pacemakers to 52 and 56 per minute, respectively. A-V dissociation with capture beats is still present. There is no change in the direction of the P waves as is noted after administration of atropine in Figure 2B.

Figure 4. Spontaneous change of rhythm on April 8. The P waves are inverted in leads II, III, aVF and V_4-V_6, and upright in I and aVR. They precede the QRS at a P-R interval of 0.24 second indicating low atrial or A-V nodal rhythm with A-V block. The QRS duration is 0.15 second with intrinsicoid deflection after 0.09 second in V_1 and after 0.06 second in V_6. This suggests the presence of right bundle branch block with probable peri-infarction block. The change of rhythm was transient as another tracing the same day again revealed A-V dissociation.

Figure 5. Bellafolline was administered orally in doses of three tablets daily from April 12 to 16. Strips *A* to *G* are cuttings from tracings obtained on April 14 to 16. All are of lead III except *D* which is of lead V_1. During A-V nodal rhythm, the P waves are inverted and precede the QRS complexes by an interval of 0.20 to 0.22 second. *A*, the two strips are continuous. A-V dissociation is present, with shifting rate of both the pacemakers. In a long tracing on this occasion the P-P intervals varied between 1.32 and 1.68 seconds and R-R intervals between 1.48 and 1.60 seconds except at one place, the second P and QRS in the lower strip. The first P in this strip just precedes the first QRS complex which is partly superimposed on the later part of the P. The second P occurs after a P-P interval of 0.90 second. Such a short P-P interval was never seen during A-V dissociation, even when the rate was considerably accelerated after the administration of atropine (Fig. 3C). This is, therefore, a premature beat arising from the upper pacemaker. A QRS complex follows after 0.22 second at an R-R interval of 1.04 seconds. The next P and QRS occur after a P-P interval of 1.60 and R-R interval of 1.54 seconds, respectively. The premature beat is apparently conducted to the ventricles and shifts the timetable of both the pacemakers. A-V dissociation continues. *B*, ventricular premature beat (fourth cycle) in A-V rhythm interferes with the upper pacemaker, causes nodal escape and sets up A-V dissociation. *C*, A-V dissociation with ventricular capture beat simulating ventricular premature beat. *D*, the two strips are continuous. Termination of A-V dissociation by interpolated premature beat (seventh cycle in upper strip) which sets up A-V rhythm. *E and F*, interpolated ventricular premature beats in A-V rhythm arising from different foci and causing prolongation of

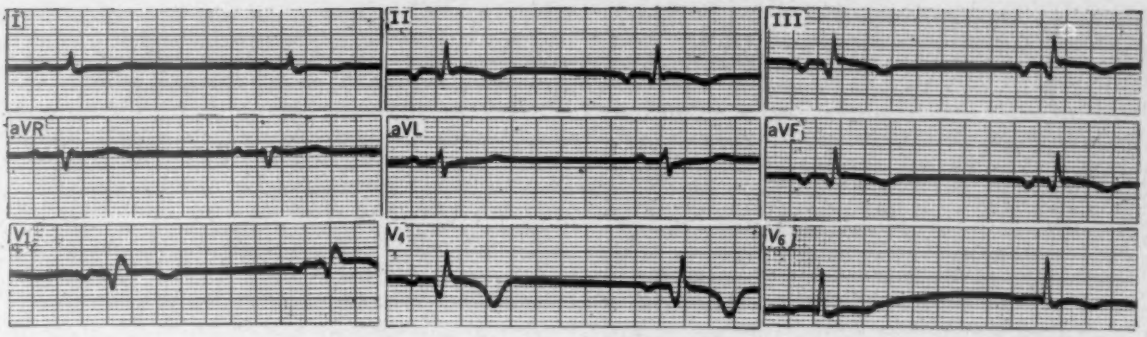

FIG. 4. Spontaneous change in rhythm on April 8, 1959. See text.

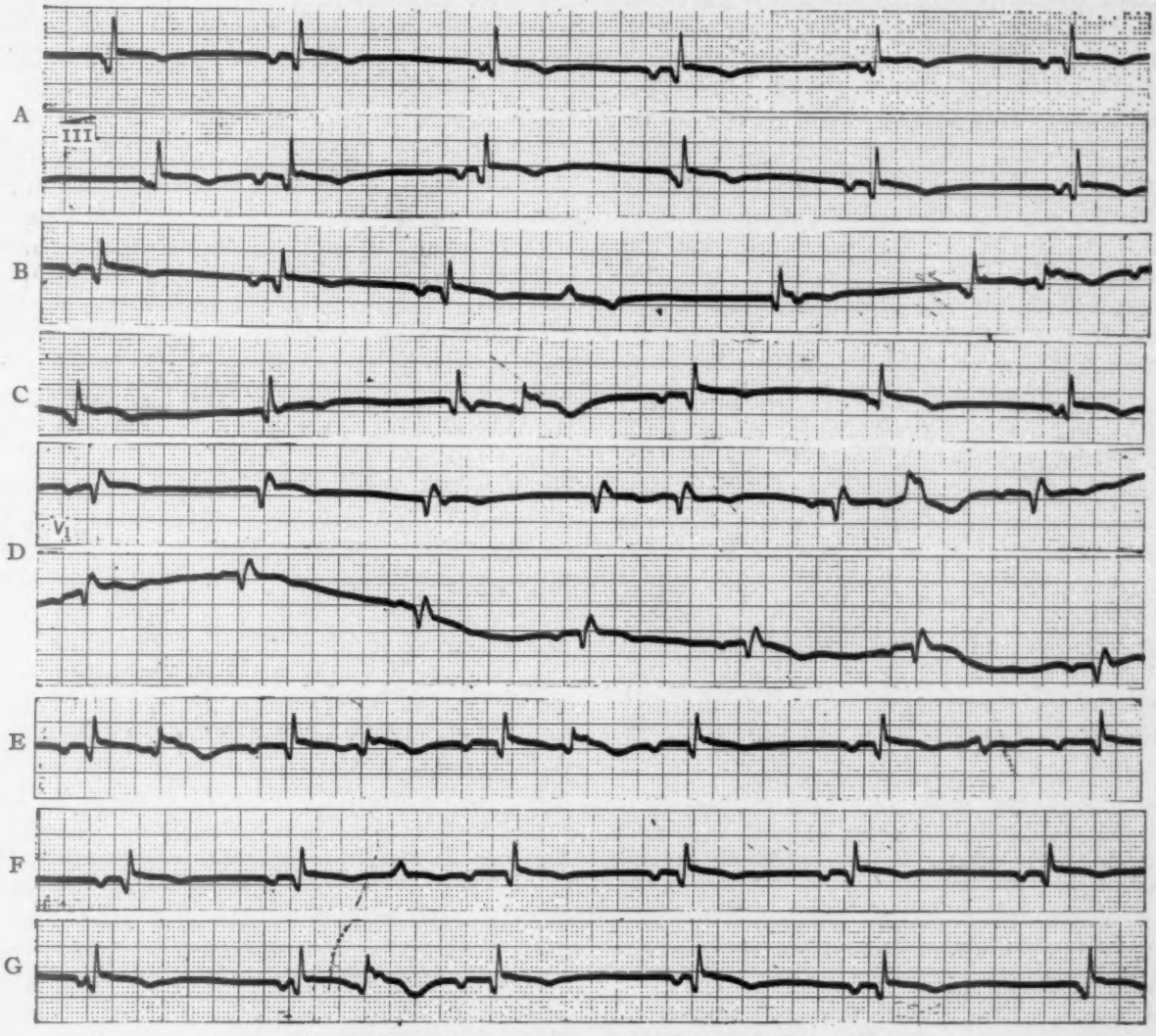

FIG. 5. Electrocardiograms taken on April 14 to 16, 1959. See text.

the P-R interval of the postextrasystolic beats. *G*, single ventricular premature beat in A-V dissociation which does not disturb either pacemaker.

COMMENTS

In all the records of this case except the one taken after the administration of atropine (Fig. 2B) the P waves are inverted in leads II, III and aVF, and upright in I and aVR. This indicates a focus either in the lower atrium near the atrial part of the A-V node or in the A-V node.[9,10] The prolonged P-R interval of the capture beats in A-V dissociation suggests the presence of first degree A-V block. Inverted

P waves in the conducted beats in Figures 4 and 5 precede the QRS complexes at a P-R interval of 0.20 to 0.24 second. This type of rhythm with a P-R interval of 0.12 second or more has been considered to represent A-V nodal rhythm with A-V block by Langendorf, Simon and Katz.[11] It has also been interpreted as coronary sinus rhythm,[1,10,12] the beats originating in the extension of the A-V node toward the area of the orifice of the coronary sinus vein, an area which has a high degree of automatism.[13] In the present case, even after the paroxysmal tachycardia subsided, the direction of the P waves remained the same during A-V dissociation as well as during A-V rhythm, during a period of nearly six weeks of further observation. This suggests that the focus for atrial activation remained unchanged. The lower pacemaker during A-V dissociation was probably located in the lower part of the A-V node. All this favors the assumption that the pacemaker during the paroxysmal tachycardia and A-V rhythm and the upper pacemaker during the A-V dissociation were situated in in the upper part of the A-V node, probably in its extension in the coronary sinus region. Upper nodal rhythm with P-R longer than 0.12 second does occur when A-V block is also present.[9] Absolute localization and distinction between low atrial, coronary sinus rhythm and upper nodal rhythm is not possible to obtain with certainty.[10]

The records also favor the assumption that there was probably complete sinus block with shift of the pacemaker to the A-V node. The possibility of permanent suppression of sinus activity by retrograde discharge by the nodal impulses seems unlikely. A regular normal sinus rhythm was never noted in this case and, therefore, the normal sinus contour of the P wave or the normal P-R interval could not be established. Positive P waves suggestive of sinus activity were observed transiently on only one occasion, in the record taken after administration of atropine (Fig. 2B) which shows A-V dissociation. This record shows wandering of the pacemaker with some P waves inverted and others positive. It is conceivable that atropine relieves the sinus block and allows the sinus pacemaker to activate the atria. It is also conceivable that the impulse may originate in the A-V node and yet be represented by a positive although abnormal P wave, an idea defended by Scherf and Shookhoff[14] many years ago and confirmed by recent experimental work. After complete elimination of the S-A node in animals, when the A-V node became the sole active pacemaker governing the heart, positive P waves in leads II, III and aVF have been found.[15]

Besoain-Santander and co-workers[16] described concealed conduction and variable penetration of the ineffective impulses, the presence of two zones of impedance in the junctional tissues and Wenckebach periods of alternate effective impulses in the lower A-V junction in atrial flutter. The arrhythmia in Figure 1 illustrates all these features and is thus analogous. The 3:1 odd conduction ratio in the presence of Wenckebach periods of alternate effective impulses is most unusual. The baseline between the P waves is, however, isoelectric and the atrial rate, the varying degree of A-V block, the increase in the block after carotid sinus pressure and the persistence of the tachycardia for several weeks are findings similar to those described in the 'hybrid' arrhythmia of paroxysmal atrial tachycardia with block.[17] A-V nodal tachycardia with concealed conduction, Wenckebach phenomenon and irregular beating of the atria and the ventricles has been described[9] but the combination of the various features in this case is unique.

Figure 2A shows a bigeminal rhythm with inverted P waves sandwiched between two QRS complexes of identical contour and an R-P interval of 0.50 second. This is suggestive of reciprocal rhythm with A-V block. Figure 2B, taken soon after 2A and following an injection of atropine, shows A-V dissociation. Again, Figure 3B shows occurrence of similar bigeminy during A-V dissociation. Furthermore, during A-V nodal rhythm in Figure 4 the P waves precede the QRS complexes by an interval of 0.24 second. There is, therefore, little doubt that the bigeminy represents A-V dissociation with escape-capture sequence. Escape-capture bigeminy associated with complete sinus block does not seem to have been reported previously although a few instances associated with 2:1 or 3:1 S-A block have been reported.[10,18–21]

S-A Block and Interference Dissociation: Miller and Sharrett[22] described the theoretic possibilities concerning the foci between which interference dissociation could occur, including dissociation between two pacemakers situated within the A-V junction. Records in Figures 2 and 3 illustrate this latter type of dissociation. It has been produced experimentally and the

possibility of such an arrhythmia occurring in specific cardiac tissue has been considered.[23] Only five cases of this arrhythmia have, however, been reported.[2–5] The rates of the upper pacemaker in the reported cases have varied between 44 and 86 per minute and are, therefore, slow in comparison to the rate in nonparoxysmal A-V nodal tachycardia.[24] The arrhythmia in two cases[2,5] was due to enhancement of activity of the A-V centers by digitalis intoxication. In cases with slower rates the arrhythmia is believed to represent marked depression of the sinus node as a result of true sinus depression or some degree of S-A block.[5] In the present case digitalis was not administered. The rate of 22 of the upper pacemaker in Figure 2A is very slow and the lowest so far reported. Sinus bradycardia with a rate of as low as 24 has been reported to occur as a result of ischemic changes or occlusion of the artery supplying the S-A node.[25,26] In order to obtain rhythms with bradycardia Scherf[27] had to damage the sinus node and depress the A-V node as well. A-V rhythm with a slow rate may result if the sinus node has ceased to function or is so slow that the A-V centers are able to escape; this form is seen in complete sinus block or when a pathologic process in the area of the sinus node has depressed it abnormally, the most common cause being occlusion of the artery supplying the sinus node.[1] It has been stated that this form of coronary sinus rhythm is rare if, indeed, it exists at all.[1] In the present case in the presence of extensive myocardial infarction and other disturbances of conduction the S-A block is probably due to a pathologic process in the area of the sinus node. Marked depression of the junctional tissues due to vagus tone is demonstrated by the acceleration of both the pacemakers after administration of atropine. Figures 4 and 5 in the present case may be interpreted to represent this rare type of slow coronary sinus rhythm.[1] Figure 3, which shows abolition of ventriculophasic sinus arrhythmia by atropine, supports the view that the vagus tone is a factor in producing this irregularity.[28–30]

Premature Beats in A-V Nodal Rhythm: Occurrence of nodal rhythm attributed to increased irritability of the A-V node[26] and of A-V nodal extrasystoles[31] after administration of atropine has been reported in cases of sinus bradycardia. There are few clinical reports describing the effect of premature beats on A-V rhythm.[6–9] Experimentally, Rothberger and Winterberg[32] and Lewis, White and Meakins[33] investigated this problem and the conditions prevailing in extrasystolic arrhythmia in A-V rhythm were further clarified by the work of Scherf and Shookhoff.[34] Figure 5 illustrates occurrence of A-V nodal rhythm and of premature beats, many of them interpolated, during administration of Bellafolline. It also illustrates disturbances of impulse formation and impulse conduction in A-V rhythm and in A-V dissociation caused by concealed conduction[35,36] and variable penetration of the junctional tissues by the premature beats. Ventricular premature beats cause change from A-V rhythm to A-V dissociation and vice versa (strips B and D). Strip A is of interest in that the premature beat arises in the upper A-V nodal pacemaker during A-V dissociation and that it shifts the timetable of both the pacemakers; A-V dissociation then continues. Another interesting feature in this record is the occurrence of interpolated ventricular premature beats during A-V nodal rhythm. The beats cause prolongation of the P-R interval of the post-extrasystolic A-V beats. The prolongation was related to the ratio between the coupling of the premature beat to the preceding QRS complex and the R-P interval between the premature beat and the next P wave.

Summary

A patient with myocardial infarction is reported whose electrocardiograms revealed the following: (1) S-A block with shift of the pacemaker to the upper part of the A-V node, probably in the coronary sinus area; (2) A-V nodal tachycardia with varying 2 : 1 and 3 : 1 A-V block and Wenckebach periods of alternate effective impulses; (3) escape-capture bigeminy; (4) dissociation between two pacemakers, both located in the A-V node; and (5) disturbances caused by premature beats, including interpolated ones, in A-V rhythm and A-V dissociation.

Acknowledgment

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, kindly permitted the publication of this report.

References

1. Scherf, D. and Gurbuzer, B. Further studies on coronary sinus rhythm. *Am. J. Cardiol.*, 1: 579, 1958.
2. Luten, D. and Jensen, J. Quoted from reference 5.
3. Schott, A. Atrioventricular rhythm with or without retrograde block. *Am. Heart J.*, 13: 61, 1937.

4. Barker, J. M. The Unipolar Electrocardiogram, p. 445. New York, 1952. Appleton-Century-Crofts.
5. Castellanos, A., Azan, L. and Calvino, J. M. Dissociation with interference between pacemakers located within the A-V conducting system. *Am. Heart. J.*, 56: 562, 1958.
6. Edens, E. Quoted from reference 10.
7. Weil, A. Quoted from reference 10.
8. Dressler, W. and Roesler, H. Premature beats in atrioventricular rhythm. *Am. Heart J.*, 51: 261, 1956.
9. Katz, L. N. and Pick, A. Clinical Electrocardiography, pp. 103, 175. Figures 46, 77, 78, 115, 180 and 181. Philadelphia, 1956. Lea & Febiger.
10. Scherf, D. and Schott, A. Extrasystoles and Allied Arrhythmias, pp. 73, 403. Figure 86. London, 1953. William Heinemann.
11. Langendorf, R., Simon, A. J. and Katz, L. N. A-V block in A-V nodal rhythm. *Am. Heart J.*, 27: 209, 1944.
12. Scherf, D. and Harris, R. Coronary sinus rhythm. *Am. Heart J.*, 32: 443, 1946.
13. Scherf, D. Upper auriculo-ventricular rhythm (coronary sinus rhythm) experimentally produced. *Proc. Soc. Exper. Biol.*, 56: 220, 1944.
14. Scherf, D. and Shookhoff, C. Quoted from reference 15.
15. Kossman, C. Advances in Electrocardiography, p. 255. New York & London, 1958. Grune & Stratton.
16. Besoain-Santander, M., Pick, A. and Langendorf, R. A-V conduction in auricular flutter. *Circulation*, 2: 604, 1950.
17. Lown, B., Wyatt, N. F., Crocker, A. T., Goodale, W. T. and Levine, S. A. Interrelationship of digitalis and potassium in atrial tachycardia with block. *Am. Heart J.*, 45: 589, 1953.
18. Padilla, T. Quoted from reference 20.
19. Holzmann, M. Clinical Electrocardiography. Figure 275A. London, 1952. Staples Press.
20. Bradley, S. M. and Marriott, H. J. L. Escape-capture bigeminy. Report of a case of A-V dissociation initiated by 2 : 1 S-A block with resulting bigeminal rhythm. *Am. J. Cardiol.*, 1: 640, 1958.
21. Sanghvi, L. M. and Banerjee, K. Escape-capture bigeminy. Bigeminal rhythm due to 3 : 1 S-A block associated with A-V dissociation. *Am. J. Cardiol.*, 4: 825, 1959.
22. Miller, R. and Sharrett, R. H. Interference dissociation. *Circulation*, 16: 803, 1957.
23. Meakins, J.; Goldenberg, M. and Rothberger, C. J. and Goldenberg, M., Gottdenker, F. and Rothberger, C. J. Quoted from reference 5.
24. Pick, A. and Dominguez, P. Nonparoxysmal A-V nodal tachycardia. *Circulation*, 16: 1022, 1957.
25. Winternitz, M. and Seyle, H. Quoted from reference 26.
26. Birchfield, R. I., Menefee, E. E. and Bryant, G. D. N. Disease of the sino-atrial node associated with bradycardia, asystole, syncope, and paroxysmal atrial fibrillation. *Circulation*, 16: 20, 1957.
27. Scherf, D. Experimental sinoauricular block. *Proc. Soc. Exper. Biol. & Med.*, 61: 286, 1946.
28. Parsonnet, A. E. and Miller, R. Heart block. The influence of ventricular systole upon the auricular rhythm in complete and incomplete heart block. *Am. Heart J.*, 27: 676, 1944.
29. Roth, I. R. and Kisch, B. The mechanism of irregular sinus rhythm in auriculoventricular heart block. *Am. Heart J.*, 36: 257, 1948.
30. Rosenbaum, M. B. and Lepeschkin, E. The effect of ventricular systole on auricular rhythm in auriculoventricular block. *Circulation*, 11: 240, 1955.
31. Pearson, R. S. B. Sinus bradycardia with cardiac asystole. *Brit. Heart. J.*, 7: 85, 1945.
32. Rothberger, C. J. and Winterberg, H. Quoted from reference 10.
33. Lewis, T., White, P. D. and Meakins, J. Quoted from reference 10.
34. Scherf, D. and Shookhoff, C. Quoted from reference 10.
35. Langendorf, R. Concealed A-V conduction: The effect of blocked impulses on the formation and conduction of subsequent impulses. *Am. Heart J.*, 35: 542, 1948.
36. Langendorf, R. and Pick. A. Concealed conduction. Further evaluation of a fundamental aspect of propagation of the cardiac impulse. *Circulation*, 13: 381, 1956.

Diagnostic Shelf

Pulmonic Insufficiency Versus Aortic Insufficiency in a Patient with Mitral Stenosis*

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THE PATIENT was a thirty-eight year old white man who, at the age of thirteen years, had had an episode of rheumatic fever accompanied by polyarthritis which left a "heart murmur."

History: The patient was asymptomatic until the age of twenty-eight, when he started suffering from exertional dyspnea, occasional palpitation and easy fatigability. Within four years he became almost completely invalided and presented the clinical picture of cardiac failure. He was then hospitalized (1954) and underwent *mitral commissurotomy*. Following this the patient had numerous episodes of "pneumonia" and pulmonary infarctions and his condition continued to become progressively worse. He was hospitalized on a few occasions and was treated with digitalis, diuretics, antibiotics and low salt diet.

Physical Examination: The patient was moderately cyanotic and dyspneic, sitting in a semi-recumbent position. The jugular veins were distended and pulsating. The pulse was 72 per minute, regular; respirations were 36 and blood pressure was 120/70 mm. Hg. There was dullness and absence of fremitus at the right base and fine crepitant rales above the area of dullness.

The maximal apical impulse was palpated in the sixth intercostal space at the anterior axillary line. There was a prominent forward thrust at the epigastrium and the whole precordial area was shaken by a heaving pulsation. There were no thrills. Auscultation revealed a grade 2 diastolic rumble at the apex preceded by an opening snap. The first sound was loud and snapping at the apex. There was a grade 2 systolic murmur, followed by a very loud (grade 5), rumbling and prolonged early-diastolic murmur in the second and third left interspaces, well transmitted across the sternum toward the fourth and fifth right interspaces, poorly along the left sternal line and not at all toward the aortic area or the apex. This murmur was not increased by inspiration. There was a grade 2, harsh systolic murmur over the aortic area followed by a weak second sound.

There was evident venous collateral circulation on the abdominal wall. The lower margin of the liver was palpable 5 finger-breadths below the right costal border. There was a shifting dullness, suggesting ascites. The femoral and pedal pulses were weak and there was marked pedal edema.

The clinical diagnosis was mitral stenosis and possible insufficiency; pulmonary hypertension; pulmonic insufficiency (Graham Steell murmur?).

Laboratory Studies: Blood culture on repeated occasions was negative. Radioactive iodine thyroid tracer study was within the normal range. Hemoglobin was 12.2 gm.; blood urea nitrogen was 29 mg.; creatinine, 1 mg.; bilirubin, total: 3.1 mg. per cent; direct: 0.95 mg. per cent; cholesterol, 174 mg. per cent. Serum enzymes were within normal limits. Urinalysis showed a trace of protein, a few red blood cells and granular casts in the sediment.

Electrocardiogram: There was severe right

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FIG. 1. Phonocardiogram in the second left interspace. The large diastolic murmur (DDd) was attributed to pulmonic insufficiency.

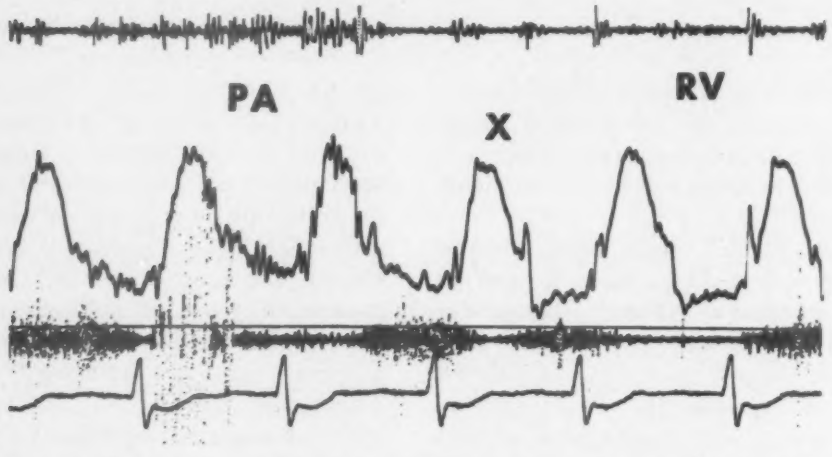

FIG. 2. Pullback of the catheter from pulmonary artery (PA) to right ventricle (RV). (X) marks the crossing of the valve. The diastolic pressure of the artery (100/31 mm. Hg) is very low when compared to that of the ventricle (104/19), confirming pulmonic insufficiency.

axis shift (+115°); atrial fibrillation with slow ventricular response; depressed S-T in leads II, III, aVF and V_2 to V_6; elevated S-T in aVR, aVL and V_1. A QR complex was present in V_1 and a qRS complex in V_6 (right bundle branch block pattern).

Phonocardiogram and Pulse Tracings: Apex. There was an opening snap 0.08 second after the aortic component of the second sound, followed by a diastolic rumble. The Q-1 interval measured 0.08 second. *Third left interspace.* A large series of vibrations were seen in diastole, starting with the second sound, first increasing, then decreasing and lasting until the next first sound. Similar tracings were recorded at the first and third left interspace (Fig. 1). *Aortic area.* A minimal systolic murmur, minimal early diastolic murmur and a weak second sound were noted. *Hepatogram and jugular tracings.* There was a normal pattern, except for lack of the *a* wave; there was no evidence of tricuspid insufficiency.

X-ray Examination: Extreme enlargement of the cardiac shadow was noted, chiefly of the left atrium and the right ventricle. The left ventricle was less markedly enlarged than the other chambers. There was a severely enlarged pulmonary artery. A calcified mitral valve was visible. Kerley lines were present in both lower lung fields. *Fluoroscopy* revealed a "hilar dance" and large pulsations of the main pulmonary artery; the pulsations of the aortic knob were small.

Right Heart Catheterization: (October 29, 1958; Illinois Research Hospital). No evidence of left to right shunt was found. Systemic arterial oxygen saturation was 85.2 per cent; right atrial mean pressure was 15 mm. Hg; right ventricular pressure, 94/15; pulmonary artery

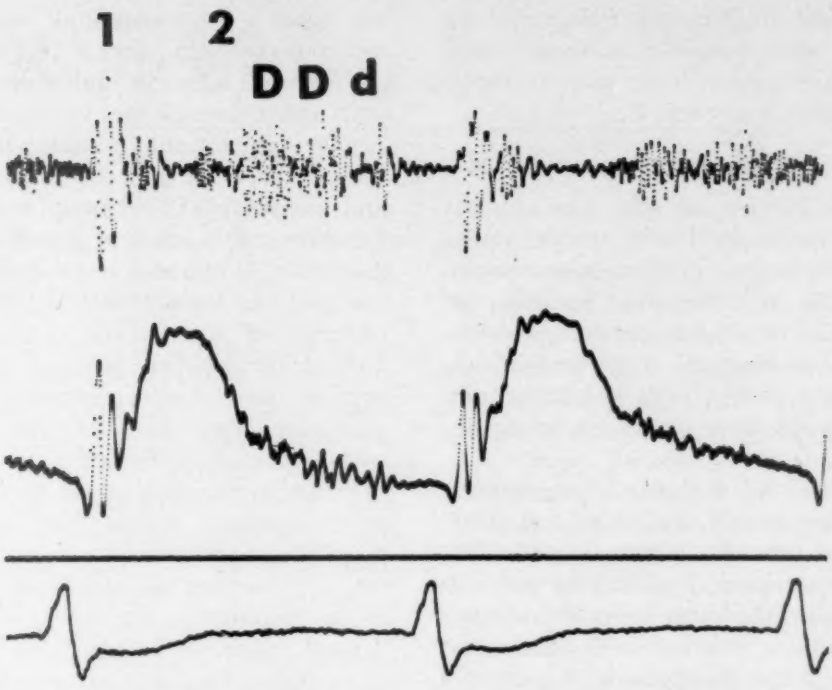

FIG. 3. Intracardiac phonocardiogram from pulmonary artery (above); pressure pulse of the artery (center); electrocardiogram (below). The large diastolic murmur within the artery (DDd) is caused by pulmonic insufficiency. The collapse of the pulse is rapid, there is no appreciable dicrotic wave and there are multiple vibrations in the diastolic section of the pulse curve.

pressure 94/28 (mean, 52), pulmonary wedge pressure, 32 mm. Hg; cardiac index, 1.5.

Right Heart Catheterization: (April 8, 1960; Mount Sinai Hospital). There was no evidence of left to right shunt. Arterial blood oxygen saturation was 82.5 per cent. Mean right atrial pressure was 20 mm. Hg. There was severe right ventricular and pulmonary hypertension with right ventricular pressure of 104/19 and pulmonary artery pressure of 100/31 (mean, 66). The low diastolic gradient between the pulmonary artery and right ventricle was interpreted as evidence of pulmonic insufficiency (Fig. 2). The wedge pressure tracing was not reliable. Intracardiac phonocardiography revealed a large diastolic murmur within the pulmonary artery (Fig. 3).

Course: Upon admission to the Mount Sinai Hospital, the patient was given Aldactone and chlorothiazide. The response in sodium excretion was satisfactory but the urinary output did not increase to any significant degree. The digitalis and antibiotic therapy was continued. Thoracentesis and paracentesis were performed in order to give the patient some symptomatic relief from the extreme dyspnea at rest. However, the patient's condition continued to deteriorate rapidly and he died on May 19, 1960.

Autopsy Findings (Dr. Krainer): The heart was huge and weighed 600 gm. The apex was formed by the right ventricle. The pericardial sac was obliterated by widespread adhesions. The tricuspid valve was dilated (120 mm. circumference). The right ventricle was dilated and hypertrophied (11 mm. thick). The pulmonic valve was delicate and of normal appearance. The pulmonic ring measured 85 mm. (normal, 71 mm.; average for a 600 gm. heart, 82 mm.). The left atrium was enormously dilated. The mitral valve was extremely stenotic and had fibrotic and calcified leaflets reducing the opening to less than 1 cm.^{2} A brown line corresponded to the surgical fracture. The left ventricle was slightly dilated; its wall was not hypertrophied (10 mm. thick). The aortic valve showed some cusp fusion at the commissures with thickening, retraction and calcification. Its ring measured 55 mm. The pulmonary arteries showed severe atherosclerotic thickening with multiple plaques. The liver weighed 650 gm. and had an increased consistency.

Conclusion: Findings were: severe mitral

stenosis with slight insufficiency; slight calcific aortic stenosis with possible minimal insufficiency; adhesive pericarditis; severe atherosclerosis of pulmonary arteries.

Comments

The clinical picture of this case clearly revealed that there still was severe mitral stenosis, in spite of the previous commissurotomy. It was impossible to decide whether this was due to restenosis or incomplete commissurotomy.

The extreme pulmonary hypertension was attributed to both mitral stenosis and arteriosclerosis of the pulmonary arterioles, confirmed by autopsy.

The extremely loud and rumbling diastolic murmur over the second and third left interspaces resembled that of a patent ductus. The loudness and roughness of this murmur; its transmission toward the lower right precordium; the lack of a similar murmur over the second right interspace; the fluoroscopic evidence of "hilar dance" while there was a small, poorly pulsating aortic knob and there was no increase of the systemic pulse pressure, led to the diagnosis of *pulmonic insufficiency*. This was confirmed by right heart catheterization. In addition to severe right ventricular and pulmonary hypertension, catheterization revealed right ventricular failure. It also showed a large pulmonic pulse pressure and a low pulmonic diastolic pressure, so that although systolic pulmonic pressure was 100 mm Hg, diastolic pulmonic pressure was 31 mm. Hg, only 12 mm. above the diastolic pressure of the left ventricle. The recording of the diastolic murmur within the pulmonary artery further confirmed the interpretation.

The downhill course of the patient advised against left heart catheterization and a new surgical commissurotomy.

Pulmonic insufficiency can be of one of the following types: (1) congenital (rare); (2) rheumatic (extremely rare); (3) bacterial (rare); or (4) that due to pulmonary hypertension with dilatation of the valvular ring (a well-known form is that causing the *Graham Steell murmur*, even though this is usually soft, faint, and variable). (5) It may be due to fibrosis of the pulmonic leaflets as a result of long lasting pulmonic hypertension (a similar explanation was given by Luisada and Wolff for the diastolic murmur of their three cases,[1] although unfortunately without autopsy evidence). The present case was interpreted as having a pulmonic insufficiency of type (4) or (5), and catheterization confirmed it.

Postmortem examination revealed a moderate aortic stenosis which had escaped clinical detection, possibly with a minimal aortic insufficiency; a severe mitral stenosis; arteriosclerosis of the pulmonary arterioles; and a minimally dilated pulmonic ostium with delicate leaflets. It is unfortunate that no attempt was made to submit the pulmonary artery to a pressure of 100 mm. Hg and to measure the ostium in such a state.

In view of the catheterization data, the character and loudness of the murmur, the x-ray data and the lack of increase in pulse pressure in the systemic circulation, the final conclusion was that the murmur was produced by pulmonic insufficiency, relative in type and caused by pulmonary hypertension. Whether the murmur should or should not be called a Graham Steell murmur is a purely semantic problem. However, in view of the peculiar characteristics of this murmur, we would prefer not to use this term.

Reference

1. Luisada, A. A. and Wolff, L. Significance of pulmonary diastolic murmur in cases of mitral stenosis. *Am. J. M. Sc.*, 209: 204, 1945.

Book Reviews

Electron Microscopy of Cardiovascular System, by Bruno Kisch, translated from German by Arnold I. Kisch. Charles C Thomas, Springfield, 1960, pp. 180, $7.50.

When a new monograph appears, written by an author who has distinguished himself by zealous explorations in many fields, one expects the very best. One is not disappointed in this latest monograph excellently translated from the German. The present treatise contains some new material made available through steady improvements in the still difficult application of electron microscopy to the circulatory system. Therefore, as the author points out, "this volume does not pretend to be a definitive monograph on a well defined subject" but rather "a summarizing presentation of work done to date."

The book follows the German text which it was the privilege of the present writer to review favorably (*Circulation Res.*, 5: 693, 1957). It deals basically with the ultramicroscopic structure of cardiac muscle fibers, cardiac nerve terminals and capillaries. The volume should be useful to physiologists and cardiologists interested in correlating various aspects of cardiac function with ultra-architecture.

The author of the monograph is aware of the danger of drawing functional inferences from static pictures of electron micrographs; hence, one will expect some difference of opinion in this area. For example, some will wish for more chemical and metabolic evidence that the tremendous capacity of the heart for sustained work is solely determined by the number and types of sarcomeres present. Also, if so-called "axon reflex effects" are indeed operative in the heart—of which the reviewer is not convinced—it appears that more distant fibers must be excited by transaxonal stimulation of adjacent nerve filaments rather than by recurrent impulses at bifurcations which do not exist. However, electron microscopic studies must be extended to epidermal structures before the classical concept of axon reflexes can be regarded as invalid for the entire body. Furthermore, one wonders whether the observed proximity of many nerve filaments to capillaries is sufficient evidence for the conclusion that ischemic pain results from their stimulation by substances conveyed by the blood stream rather than by products of metabolism, for which there is also considerable evidence.

None of these quibbles over interpretation detracts from the basic intent of the monograph, which is to supply the ultra-architecture underlying functions that must be finally established by other means. This English edition with its clear descriptions and superb illustrations should serve to simulate further interest in the application of electron microscopy to the cardiovascular system in health and disease.

CARL J. WIGGERS, M.D., SC.D., F.A.C.C.

Missbildungen des menschlichen Herzens-Entwicklungsgeschichte und Pathologie, by H. Barthel. Georg Thieme Verlag, Stuttgart, 1960, pp. 240, DM 188, $44.75.

The ever increasing importance of congenital malformations of the heart makes the appearance of this book on the normal and pathologic embryology of the heart most welcome. The combination of a lucidly and comprehensively written text, amply supplied with 215 excellent illustrations and a superb printing job, makes Barthel's book required reading for cardiologists, cardiac roentgenologists and cardiac surgeons.

The predominantly diagrammatic approach to the normal development of the heart is particularly convenient to the nonanatomist and nonembryologist who merely wants to learn of the predominant present day concepts and the facts, as known, without getting too deeply involved with the prevalent controversies. The pathologic embryology of cardiovascular malformations is presented in a masterly fashion. The abundant use of colored illustrations makes for an easy identification and classification of all the known congenital malformations. Discussions are concise but adequate and the bibliography provided is extensive. The superb quality of Miss I. Schamburg's illustrations have greatly contributed to the success of the book. It is highly recommended.

ARTHUR GRISHMAN, M.D.

Grundriss und Atlas der Elektrokardiographie, 3rd ed., by Rudolf Zuckermann. Georg Thieme Verlag, Leipzig, 1959, pp. 660, DM 72.15.

Zuckermann's book contains two independent sections: a synopsis of basic electrocardiographic patterns and an atlas of normal and abnormal electrocardiograms. The text in this, the third edition, has been enlarged and electrocardiograms are also described from a vectorial point of view. Numerous new electrocardiograms have been added to the atlas, along with x-ray pictures, phonocardiograms, pulse and pressure tracings and autopsy findings.

The plan of the text is conventional. There is material on the spread of the stimulus through heart muscle, bipolar and unipolar lead systems, and basic vectorcardiographic patterns. Chapters on the normal electrocardiogram, ventricular hypertrophy, bundle branch block, myocardial infarction, pericarditis, cor pulmonale and congenital heart disease follow. There is also a section on the arrhythmias.

Zuckermann describes the following interesting electrocardiographic classification of congenital cardiac lesions:

I. Pure right strain—enlargement of the right atrium and right ventricle:

1. Tetralogy of Fallot
2. Pulmonary stenosis
3. Complete transposition of the pulmonary veins
4. Right to left ductus
5. Mitral and aortic atresia
6. Taussig-Bing complex
7. Aortic isthmus stenosis or atresia, with a distal right to left ductus

II. Predominant right strain—enlargement of both atria and of the right ventricle. The enlargement of the left atrium is not always observable:

1. Transposition of the great vessels
2. Atrial septal defect
3. Lutembacher syndrome
4. Pentalogy of Fallot
5. Common ventricle
6. Congenital mitral stenosis
7. Aortic isthmus stenosis with atrial or ventricular septal defect, or proximal left to right ductus

III. Bilateral strain—bilateral ventricular enlargement with right, left, or bilateral atrial enlargement:

1. Ventricular septal defect
2. Eisenmenger complex
3. Left to right ductus with pulmonary hypertension.
4. Trilogy of Fallot
5. Aortic-pulmonary fistula
6. Truncus arteriosus
7. Pulmonary stenosis with ventricular septal defect

IV. Predominant left strain—enlargement of the left ventricle with right or bilateral atrial enlargement:

1. Tricuspid atresia
2. Common ventricle

V. Pure left strain—enlargement of the left ventricle and left atrium:

1. Left to right ductus without pulmonary hypertension
2. Aortic isthmus stenosis
3. Aortic and subaortic stenosis

VI. Normal electrocardiogram—the defect is associated either with a normal electrocardiogram, or electrocardiographic changes occur in a late stage:

1. Left to right ductus
2. Aortic isthmus stenosis
3. Morbus Roger
4. Arteriovenous coronary fistula

VII. Special electrocardiographic patterns—the defect can often be suspected from the electrocardiogram:

1. Mirror image dextrocardia
2. Dextroversion
3. Pulmonary origin of the left coronary artery
4. Tricuspid atresia
5. High ventricular septal defect
6. Atrial septal defect
7. Transposition of the pulmonary veins
8. Common ventricle
9. Ebstein anomaly
10. Aortic stenosis
11. Common atrioventricular canal
12. Transposition of the great vessels

The atlas covers a wide range of normal and abnormal electrocardiographic patterns and contains, as well, an interesting collection of electrocardiograms of various animals. It is not integrated with the first half of the book and each case is described separately.

The first part of the book, for the most part, is brief and adequate. The atlas portion is excellent. The book is printed on good, coated paper and will prove of value to those with a reading knowledge of German.

EMANUEL GOLDBERGER, M.D.

Diseases of the Newborn, by Alexander J. Schaffer. Section on Neonatal Cardiology by Milton Markowitz. W. B. Saunders Co., Philadelphia, 1960, pp. 878.

This comprehensive text on clinical neonatology may be considered as actually two distinct volumes, the excellent section on neonatal cardiovascular abnormalities by Dr. Milton Markowitz constituting a monograph in itself.

The fifteen sections covering individual systems are broken down into chapters, each dealing with a specific abnormality or disease process. Each one is so comprehensive and complete, within the scope of this book, that it constitutes an excellent review and is liberally illustrated with photographs, case histories and multiple recent references. The format is one of uniform simplicity and the author concisely discusses each condition from the standpoint of incidence, etiology, pathogenesis, diagnosis, prognosis and treatment. The section on the cardiovascular system deviates from this format only slightly in that each specific lesion does not enjoy its own chapter but rather is conveniently divided into congenital heart disease, myocarditis, arrhythmias and miscellaneous conditions with a separate chapter on treatment.

Although the book is primarily intended for pediatricians, general practitioners and obstetricians, it might well be recommended for any specialist who may have occasion to treat the newborn infant.

RAPHAEL N. PAUL, M.D.

Central Nervous System Control of Circulation. Physiological Reviews, Supplement No. 4. American Physiological Society, Washington, D. C., 1960, pp. 298.

This supplement consists of the proceedings on the central nervous system control of the circulation sponsored by the Division of Medical Sciences of the National Research Council, held in Washington, D. C., in November, 1959.

A distinguished international panel contributes its views on the complex relationships between the central nervous system and the cardiovascular system. The subject is explored in detail, including: neural mechanisms of cardiac control during exertion (Rushmer); central control of renal circulation (Pappenheimer); influence of central nervous system on veins (Burch); sympathetic control of vessels in the hand (Barcroft); role of hypothalamic structures in cardiac control (Smith); circulatory effects of cortical stimulation (Delgado); central control of cardiac function (Schaefer) and several other related topics. Discussions in depth concerning the papers presented add appreciably to the knowledge and perspective imparted by this volume.

Inasmuch as this was a conference participated in by outstanding investigators in neurophysiology and in cardiovascular physiology, discussions are on the highest level. There is no question that as a compendium of current knowledge in this complex and important area, this volume should be an invaluable reference source. The average, clinically oriented cardiologist will probably find this symposium somewhat too sophisticated for his wants with its assumption of a considerable background in neuroanatomy and neurophysiology; nor will his task be made easier by the paucity of concise, comprehensive summaries of the various chapters.

Active investigators or those interested in the field should derive great use and stimulation from this volume. The National Research Council and the American Physiological Society are to be commended for organizing and presenting to the profession the work and current thoughts of these experts.

LESLIE A. KUHN, M.D.

Cinefluorography, edited by G. H. S. Ramsey, J. S. Watson, Jr., T. A. Tristan, S. Weinberg and W. S. Cornwall. Charles C Thomas, Springfield, 1960, pp. 266, $11.75.

The Proceedings of the First Annual Symposium on Cinefluorography provides the reader with an excellent appraisal of the present technical status and medical usefulness of cinefluorography. Although many of the chapters are of a highly technical nature, they, as well as the more medically directed ones, give a clear insight into the present and future status of this relatively new technic. Little doubt can be left after having read it that cinefluorography is one of the major contributions to radiographic technics and, therefore, to the future development of diagnostic radiography. The book should be of great interest to the cardiologist and radiologist alike. It is well edited, most informative, and the printing and reproductions are of excellent quality.

ARTHUR GRISHMAN, M.D.

College News

PRESIDENT'S COLUMN

The Identification of Excellence

THE AMERICAN COLLEGE of Cardiology has enjoyed a remarkable growth and when one attempts to analyze this success certain significant ideas and landmarks can be identified. Among these have been the American Journal of Cardiology, the Fireside Conferences, the Workshops and the Annual Meeting. The final reason for the success of the College has been the simple fact that there was a need for such a College . . . a gathering point for men and women sharing the same professional enthusiasm . . . an organization *of* physicians and *for* physicians . . . whose function would be that of offering an *identification of excellence* and a *stimulus toward excellence*. And as must be true for a College, those entering must answer to a standard of preparation. As a College, levels for advancement must be identified and finally, a College must have dignity and moments of ceremony. Each of these duties has been met and we can take satisfaction in the admission standards, the advancement requirements, and the Convocation Ceremonies . . . we are indeed a College.

The College has, in May, enjoyed the good fellowship and stimulation of its Annual Meeting and Convocation. This ended the tenth year of the College and certain events of this meeting made one aware of the potentials of our organization. These events were, first, the total enrollment of 1287 physicians. This is a sobering figure . . . almost 1300 physicians chose our Annual Meeting as the forum at which they would exchange information. Such a figure cannot be ignored . . . the quality of the program represents the honor and the responsibility of the College; persistent effort and imagination must continue to go into these programs.

The final experience at the May meeting which made one aware of the maturity of the College was the Convocation. Present here as Fellows or being inducted into the College was an exciting percentage of the cardiovascular physicians and surgeons of our time. Here was indeed evidence that the College was serving as a gathering place for good fellowship—and for the identification of excellence.

E. GREY DIMOND, M.D., F.A.C.C.
President

Excerpts from the Proceedings of the

Tenth Annual Convocation

May 19, 1961, Biltmore Hotel, New York, New York

AWARD OF HONORARY FELLOWSHIP

Dr. Louis F. Bishop: The chair now recognizes Dr. Osler Abbott, immediate Past President of the College.

Dr. Osler A. Abbott: Mr. President, it is my great privilege to present to you Isaac Starr of Philadelphia, Bachelor of Science, Doctor of Medicine, Hartzell Research Professor of Therapeutics of the University of Pennsylvania, Consultant to the U.S. Navy and Chairman of the National Research Council Committee on Drug Addiction, Chairman of the American Medical Association's Council on Drugs, and the recipient of the U.S. Selective Service medal.

Dr. Starr was born in 1895 and received his B.S. degree from Princeton University, magna cum laude in 1916. After receiving his doctorate in medicine from the University of Pennsylvania in 1920, he became house officer at the Massachusetts General Hospital and then returned to his alma mater, the University of Pennsylvania, to become an instructor in pharmacology; in 1928 he was advanced to the rank of assistant professor and then in 1933 became the Hartzell Research Professor of Therapeutics, a chair which he now holds. Dr. Starr was dean of the School of Medicine during the years 1945, '46, '47 and '48.

During the Second World War, Dr. Starr served as the active chairman on several subcommittees on pharmacy, on essential drugs, on medical supplies, and on the National Research Council. He took part in the investigations in aviation medicine and on an antimalarial drug. Since the war he has been active in the National Research Council's Committee on Narcotics and Drug Addiction, and was chairman of the committee for a period of thirteen years. He is also interested in problems of alcohol and is a member of the cardiovascular study section of the National Institute of Health. For the American Medical Association he served as a member in the council of drugs since 1945, and since 1960 has been chairman of the council; he received the Albert Lasker award of the American Heart Association in 1957.

My candidate, Mr. Chairman, has to his credit over ninety publications, largely in the field of the diagnosis and therapy of cardiac conditions, peripheral vascular disease, congestive failure and the relief of pain. By far his most important work has been his study of the *ballistocardiograph* and his name will always be associated with the development of that particular diagnostic instrument. He has done extensive work in the utility of the ballistocardiogram, its relation to the pulse and to aspects of cardiac function such as output, work and force.

Mr. President, for these reasons, for this dedicated researcher, scholar, teacher and inspiring pioneer, the Awards Committee has recommended to the Trustees and the Trustees have by unanimous vote consented that Dr. Isaac Starr be enrolled on the roster of the College in a special category, and I now ask you, Mr. President, that you confer on Isaac Starr the certificate of Honorary Fellowship.

President Bishop: Welcome, Dr. Starr. I have heard with much interest the citation that Dr. Abbott has read, and for the reasons stated therein and by virtue of the authority vested in me by the charter of our College, I confer upon you the certificate of Honorary Fellowship in the American College of Cardiology.

AWARD OF GROEDEL MEDAL

Dr. Dwight E. Harken: Mr. President, I feel that it is an honor as well as a great personal privilege to be able to present to you a man whom we have all held in great respect and affection for many years, William Bennett Bean, Bachelor of Arts, Doctor of Medicine, Fellow of the American College of Physicians, Lt. Col. of the Medical Corps, U.S. Army (Retired); Professor of Medicine and head of the Department of Internal Medicine, State University of Iowa in Iowa City; senior medical consultant, Veterans Administration; lecturer, writer, editor, medical archivist and historian.

Dr. Bean was born in 1909 at Manila in the Philippine Islands. He received his B.A. from the University of Virginia in 1932, and his doctorate in medicine from the same university in 1935. He is a Diplomate of the American Board of Internal Medicine and of the American Board of Nutrition; a member and a fellow of more than thirty medical and academic associations, lecturer and visiting professor to a dozen universities; author of four books, with a bibliography of publications that contains 239 titles of the widest possible variety of medical and cultural topics.

Dr. Bean interned at Johns Hopkins Hospital after his graduation from the University of Virginia School of Medicine; he began a long career of training and teaching including posts at the Boston City Hospital, Thorndike Memorial Laboratory, Harvard University and the University of Cincinnati College of Medicine where he attained the rank of associate professor. He moved to his present post in Iowa in 1948 where he has been professor and head of the department of internal medicine. During World War II he was director of the Armored Medical Research Laboratory at Ft. Knox, Kentucky. In addition to accomplishing many fundamental pieces of research, he has served on the editorial boards of the Cincinnati Journal of Medicine, Nutrition Reviews, Journal of

Clinical Investigation, and the Journal of Laboratory and Clinical Medicine. He is now on the editorial board of the A.M.A. Archives of Internal Medicine.

My candidate, Mr. President, has a quality of gentle humor that is rare in a great doctor. He has a gift of elegant and succinct expression and the slant of his medical thinking can best be set down in his own words, which are quoted from a letter that he wrote: "My medical interests are eclectic and universal. In addition to cardiology, nutrition and liver disease, my favorite hobby is deflating stuffed shirts." Dr. Bean has been known for many years as the defender of the painstaking observation, of the unhurried effort, of the uncompromising standard of excellence. As a critic, he is feared, but as a scholar he is honored.

Mr. President, the Awards Committee has recommended and the Trustees have unanimously concurred that William Bennett Bean be awarded the Groedel Medal for 1961 and be appointed Groedel Lecturer for this convocation.

President Bishop: Thank you, Dr. Harken. Welcome, Dr. Bean. I bestow on you the highest award of the College, the Groedel Medal, and in compliance with the unanimous vote of the Board of Trustees you are hereby appointed Groedel Lecturer for this convocation.

INDUCTION OF NEW PRESIDENT

President Bishop: It is now my duty to relinquish the gavel to Dr. E. Grey Dimond, the President-Elect of the College, who has served a strenuous year of apprenticeship. He will take the helm of our organization for the year of 1961–1962. I wish at this time to give my heartfelt thanks to the officers, trustees and committee chairmen who have done so much the past year to make my administration a pleasant and rewarding experience.

Ladies and gentlemen, I now present the President of the American College of Cardiology, Dr. E. Grey Dimond.

Announcements

Robert P. Glover Memorial Fund

When the chapter organization of the American College of Cardiology was discontinued, the various chapters throughout the country returned their balance funds to the general treasury. This week we have received in the Central Office of the College the balance of $310.00 which remained in the Pennsylvania chapter and there is a request that it become the nucleus of an endowment in the name of our Past President and Honorary Trustee, Dr. Robert P. Glover, the proceeds of the endowment being used to further the educational purposes of the College.

This wish of the Pennsylvania chapter to memorialize one of the most energetic and beloved of the builders of the College was announced at the Tenth Anniversary Business Meeting, and a number of the Fellows came forward and expressed a willingness to contribute to the Glover Memorial Fund so as to build it up into the required proportions as rapidly as possible.

Photographs of the Tenth Annual Convention

Many of the Fellows at the Tenth Annual Convention were busy with their cameras and flashbulbs, taking candid shots of the various activities that were going on. In former years some of these candid shots were sent to the Central Office and became part of a valuable scrap book in our College Archives. It is hoped that this year the Central Office will again receive a donation of prints of candid photographs for our scrap book. The College now has an official historian and you may be sure that the snapshots will remain in the College Office with a notation not only of the subjects of the shots themselves but also of the donor of the prints.

Young Investigator's Award

At the annual Convocation of the College on May 19, 1961 the Young Investigator's Award, consisting of a silver medal, a certificate and a prize of $1,000 was presented to J. H. Mitchell, M.D., National Heart Institute, Bethesda, Maryland, for his investigation on "The Transport Function of the Atrium." Honorable mention, consisting of a $200.00 prize, was awarded to D. M. Long, Jr., M.D., University of Minnesota, Minneapolis, Minnesota, for his investigation on "Myocardial Necrosis and Electrocardiographic Changes Related to Microcirculatory Abnormalities." Each of the eight other finalists received $100.00 as a consolation award.

Registration at Convention

The following is a tabulation of the attendance at the Tenth Annual Meeting held May 17 to 20, 1961 in New York City.

Fellows of the College	506
Associate Fellows of the College	198
Nonmember Physicians	583
Total	1,287

This does not include wives, exhibitors, medical students, technicians and other guests, a total of 385.

PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of **THE AMERICAN JOURNAL OF CARDIOLOGY** welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to **THE AMERICAN JOURNAL OF CARDIOLOGY**; material is copyrighted and may not be reproduced without permission of the publishers.

Preparation of Manuscripts

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editor; include staff position and connection; list bibliographic references in chronological order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical with volume, page and year. For example: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3:274, 1959.

Preparation of Illustrations

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

Reviews, Abstracts

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology**, 466 Lexington Avenue, New York 17.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

Reprints

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology**, 466 Lexington Avenue, New York 17, N. Y. Prices are quoted after articles are published.

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NEW BOOKS FOR CARDIOLOGISTS
PUBLISHED IN THE FIRST 6 MONTHS OF 1961

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☐ *Buford H. Burch and Arthur C. Miller*—**SURGICAL DISEASES OF THE LUNG.** Pub. Feb. '61, 144 pp. (6¾ x 9¾), 60 il., $8.50

☐ *E. Grey Dimond*—**THE EXERCISE ELECTROCARDIOGRAM IN OFFICE PRACTICE.** Pub. July '61, 180 pp. (10½ x 8), 338 il., $10.00

☐ *Carl Hughes and Warner Bowers*—**TRAUMATIC LESIONS OF PERIPHERAL VESSELS.** Pub. Feb. '61, 208 pp., 110 il., $8.00

☐ *Vernon M. Ingram*—**HEMOGLOBIN AND ITS ABNORMALITIES.** Pub. May '61, 168 pp., 93 il. (Amer. Lec. Living Chemistry), $7.50

☐ *Richard J. Jones and Louis Cohen*—**CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE.** Pub. May '61, 216 pp., 63 il. (Amer. Lec. Living Chemistry), $7.50

☐ *S. D. Larks*—**FETAL ELECTROCARDIOGRAPHY: The Electrical Activity of the Fetal Heart.** Pub. Dec. '60, 128 pp. (6¼ x 9¾), 70 il. (Amer. Lec. Gynecology and Obstetrics), $6.50

☐ *Esmond R. Long*—**SELECTED READINGS IN PATHOLOGY (2nd Ed.).** Pub. May '61, 316 pp. (6¼ x 9½), 25 il., $8.50

☐ *Richard H. Meade*—**A HISTORY OF THORACIC SURGERY.** Pub. Aug. '61, 960 pp., 116 il.

☐ *K. Alvin Merendino et al.*—**PROSTHETIC VALVES FOR CARDIAC SURGERY.** Pub. March '61, 616 pp., 393 il., $8.25

☐ *Sir George Pickering*—**THE TREATMENT OF HYPERTENSION.** Pub. March '61, 192 pp., 70 il. (Amer. Lec. Living Chemistry), $7.00

☐ *William S. Reveno*—**711 MEDICAL MAXIMS, Volume II.** Pub. April '61, 176 pp., $3.50

☐ *Hans Selye*—**THE PLURICAUSAL CARDIOPATHIES.** Pub. June '61, 464 pp., 287 il.

☐ *Sigmund A. Wesolowski*—**EVALUATION OF TISSUE AND PROSTHETIC VASCULAR GRAFTS.** Pub. Sept. '61, 224 pp., 88 il. (Amer. Lec. in Surgery)

☐ *Merle E. White*—**AN OUTLINE GUIDE FOR THE CARE OF POST-OPERATIVE CARDIAC PATIENTS.** Pub. May '61, 120 pp., 75 il., $6.00

☐ *Grace Wyshak*—**CARDIACS AND DIABETICS IN INDUSTRY.** Pub. Aug. '61, 272 pp., 36 il.

☐ *Benjamin W. Zweifach*—**FUNCTIONAL BEHAVIOR OF THE MICROCIRCULATION.** Pub. April '61, 164 pp., 20 il. (Amer. Lec. Physiology), $7.00

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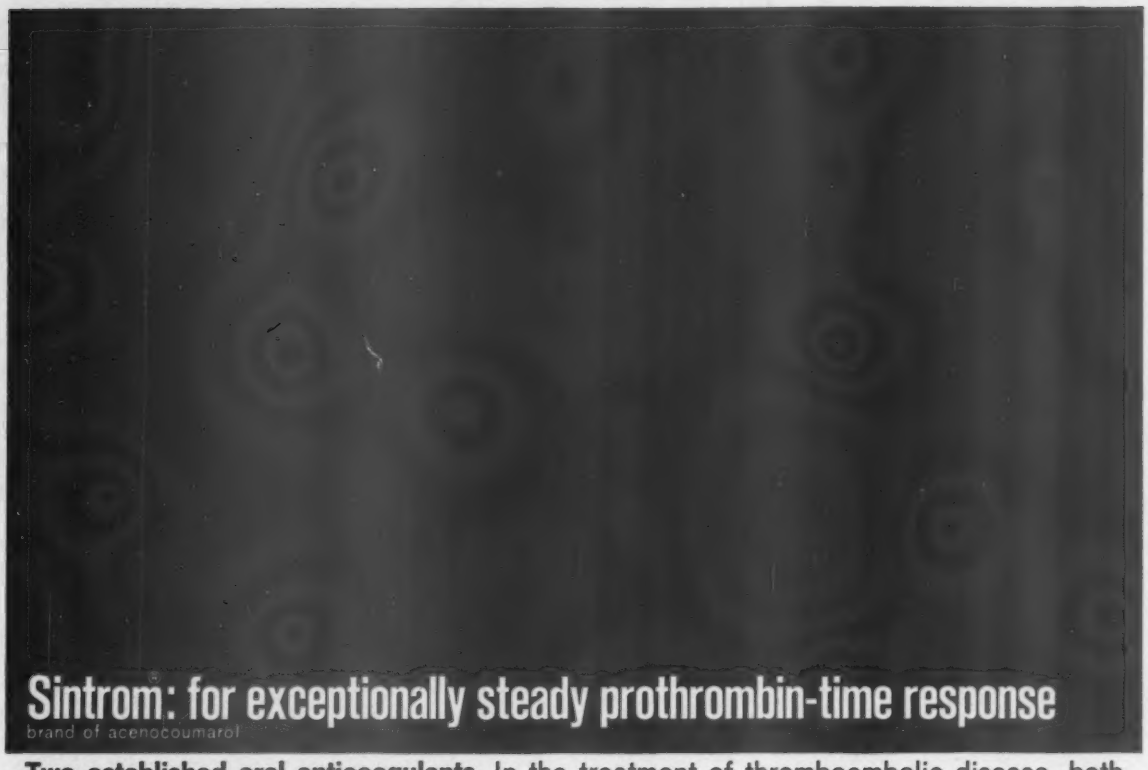

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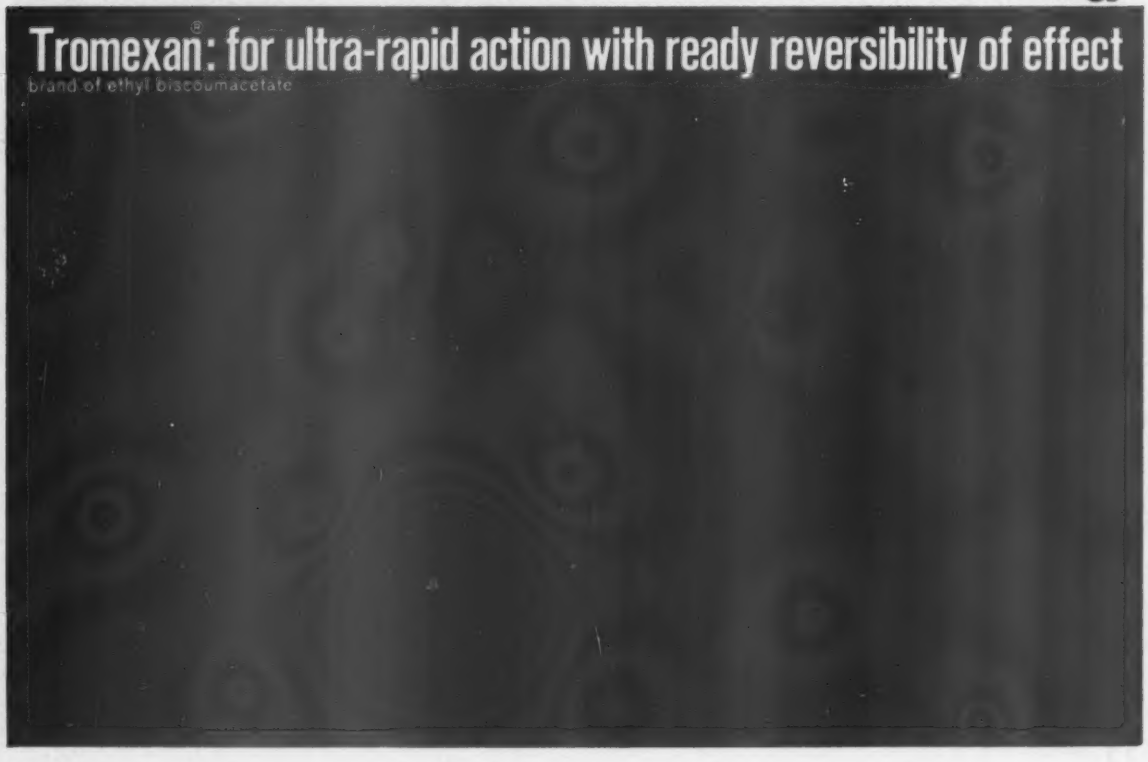

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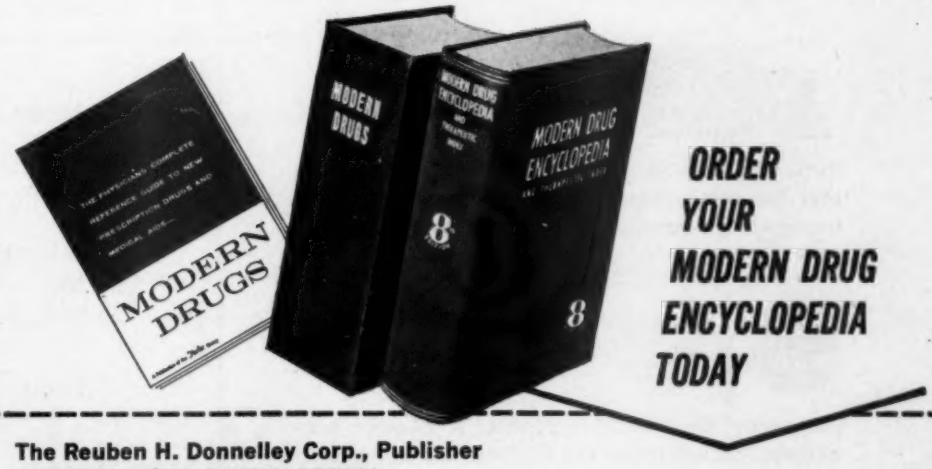

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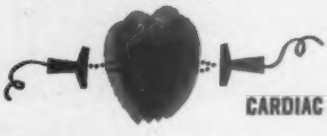

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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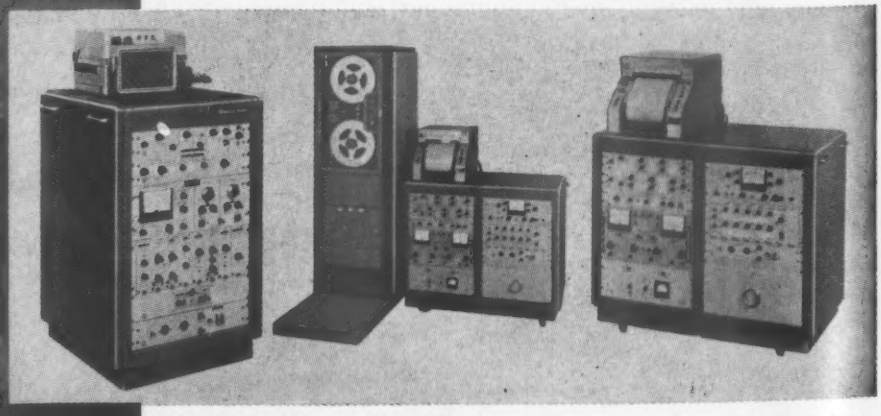

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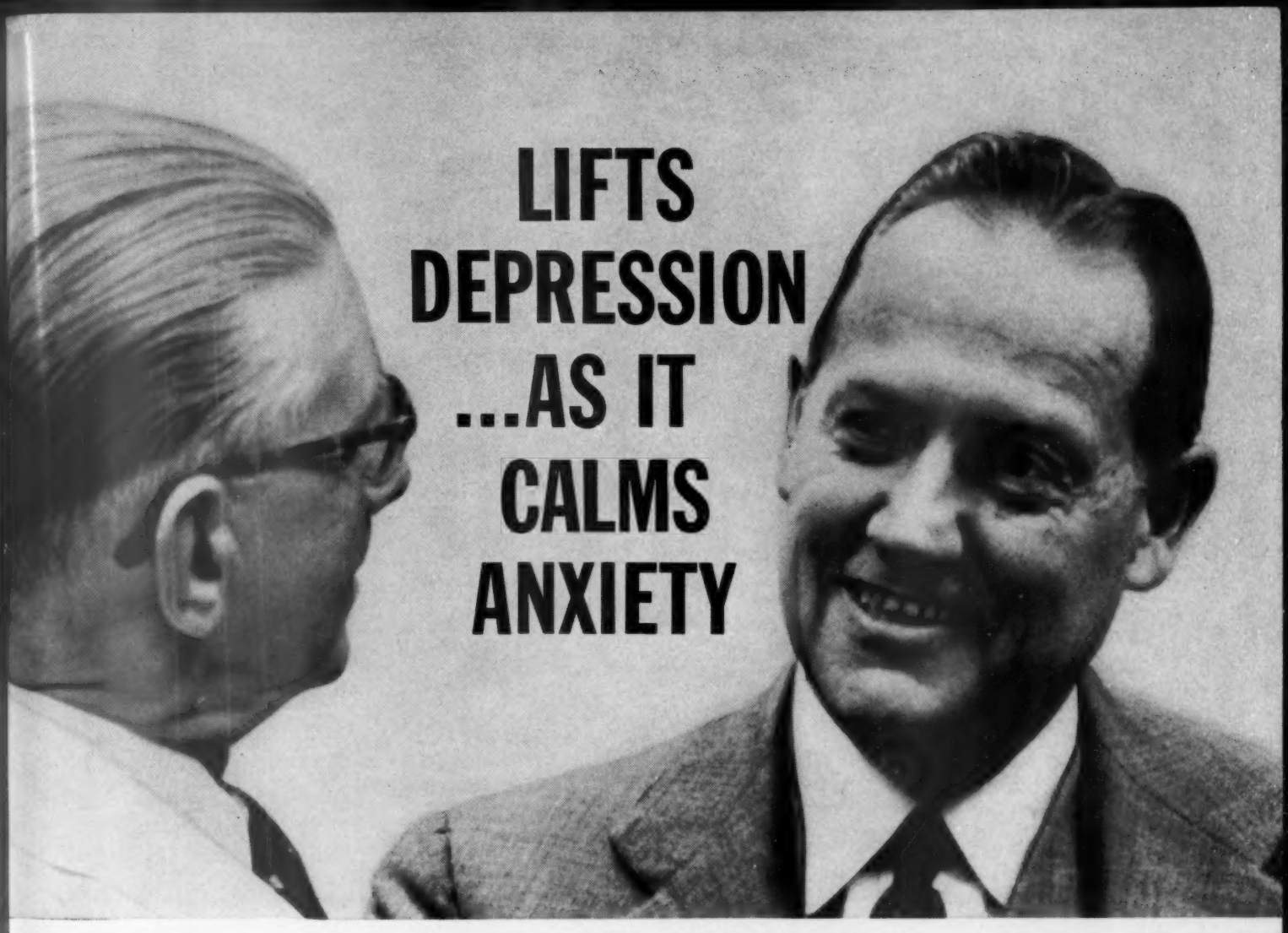

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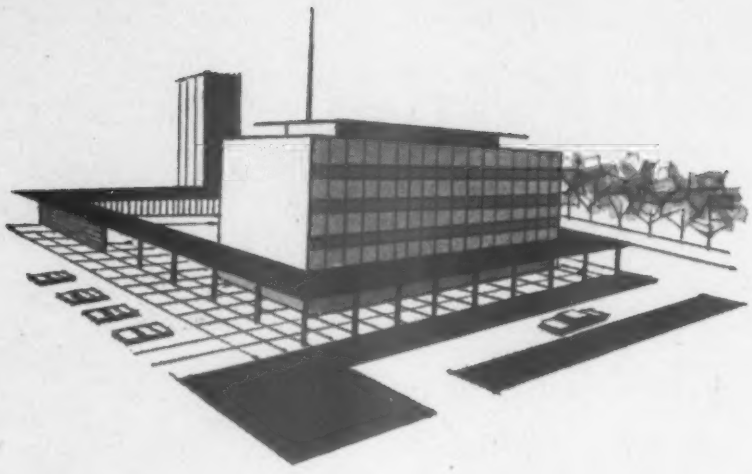

work capacity with no breakfast and a mid-morning break

The experiment* reported here had as its object to show effect of various regimens of breakfast and mid-morning breaks on maximum work output as measured by a bicycle ergometer. Twenty subjects, 18 to 36 years of age, including both office and factory workers participated. The various periods of the experiments used for the comparisons were as follows:

Period 1. Basic breakfast without mid-morning break.
Period 2. No breakfast without mid-morning break.
Period 3. Basic breakfast with mid-morning break.
Period 4. No breakfast with mid-morning break.

"The data seem to justify the following conclusions:

"All subjects did significantly more work when the dietary regimen included an adequate breakfast than when it was omitted.

"The addition of a mid-morning break when an adequate breakfast was eaten resulted in no advantage as far as maximum work output was concerned.

"The addition of a mid-morning break to a dietary regimen which omitted breakfast showed a significant advantage for half of the subjects, in maximum work output.

"The data seem to indicate that an adequate breakfast is better economy as far as capacity to work is concerned than the substitution of a mid-morning break for breakfast."

**Tuttle, W. W., Herbert, Edward: Work Capacity With No Breakfast and a Mid-Morning Break. J. Am. Dietet. A. 137:37, 1960.*

a basic breakfast† used in this experiment followed this moderate low-fat, well-balanced menu.

†A Summary of the Iowa Breakfast Studies, published by Cereal Institute, Inc., May 1, 1957.

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Fuller, H. L.: Angiology *11*:200 (June) 1960.

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*Registered trade mark. Patent applied for.

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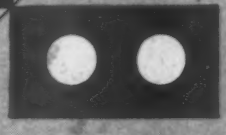

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